Cent. Eur. J. Chem. • 10(4) • 2012 • 1119-1136
DOI: 10.2478/s11532-012-0015-4

VERSITA

Central European Journal of **Chemistry**

New serinolic amino-*s*-triazines by chemoselective amination of cyanuric chloride and their (pro)diastereomerism in restricted rotational phenomena

Research Article

Oana Moldovan[1,2], Pedro Lameiras[3], Eric Henon[3], Flavia Popa[1,2], Agathe Martinez[3], Dominique Harakat[3], Carmen Sacalis[1], Yvan Ramondenc[2], Mircea Darabantu[1*]

[1]*"Babes-Bolyai" University, Department of Organic Chemistry, 400028 Cluj-Napoca, Romania*

[2]*University and INSA of Rouen, IRCOF – LCOFH, UMR 6014 CNRS COBRA, 76821 Mont Saint-Aignan Cedex, France*

[3]*University of Reims Champagne-Ardenne, ICMR - LIS, UMR 6229, BP 1039, 51687 Reims, France*

Received 4 December 2011; Accepted 23 January 2012

Abstract: The highly chemoselective preparation of new elaborated *N*-unsymmetrically substituted chlorodiamino-*s*-triazines and melamines, seen as building-blocks for iterative synthesis, is reported. It consisted of amination of cyanuric chloride with commercial C-2-substituted 2-aminopropane-1,3-diols ("*serinols*"), playing the role as "*open-chain*" unit and enantiopure (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diols ("*p-nitrophenylserinols*") based amino-1,3-dioxanes ("*closed-chain*" unit). Issued from the restricted rotation about C(s-triazine)-N(exocyclic) partial double bonds, seen as axes of (pro)diastereomerism, a global four-component rotational equilibrium involving the title compounds is discussed based on DFT computation and (VT) NMR data. Depending on π-deficiency of the *s*-triazine core, an (un)synchronised deblocking of the generated rotational diastereomers was observed. They are discussed as influence of intra- *vs*. intermolecular NH…OH (dynamic) interactions occurring in the "*open-chain*" unit and the anancomeric, axial *vs.* equatorial, amino-anchorage of the "*closed-chain*" unit.

Keywords: *Amino-s-triazines • NMR • Restricted rotation • Serinols*

1. Introduction

Following our recent findings in the synthesis [1-5], structure [1-5] and use [6-8] of *N*-substituted 2,4,6-triamino-*s*-triazines (*melamines*) by exploiting the versatile nucleophilicity of *C*-substituted 2-aminopropane-1,3-diols (*serinols*) [9,10] against cyanuric chloride, we now report new results in a combined synthetic-structural approach.

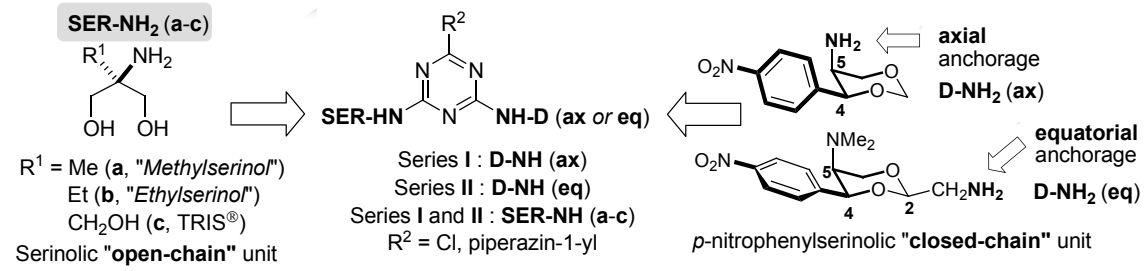
Thus, since both theoretic [11] and / or synthetic [12] advances in dendrimers' chemistry called attention on the diversity of peripheral groups providing a plethora of sites for further nanoscale manipulation of these architectures, we considered two series of new *N*-substituted amino-*s*-triazines, **I** and **II** (Scheme 1), possessing:

i) A serinolic "*open-chain*" unit of type C-2-substituted 2-aminopropane-1,3-diol, **SER-NH$_2$** (**a**-**c**).

ii) A "*closed-chain*" unit of type *O*,*O*-masked *p*-nitrophenylserinol as anancomeric (4*S*,5*S*)-amino-1,3-dioxane containing the primary amino group in axial **D-NH$_2$** (**ax**) or in equatorial **D-NH$_2$** (**eq**) position [9,10].

Although amination of cyanuric chloride is a standard synthetic protocol, the dendritic-iterative facet of this methodology was reviewed just recently by Simanek *et al.* [13-15]. Conversely, to a detailed conformational analysis in this class of elaborated amino-*s*-triazines

* *E-mail: darab@chem.ubbcluj*
darabantu@cluj.astral.ro



Scheme 1. Targeted series of amino-*s*-triazines.

attention was paid also very recently only [16] by the same authors in spite of the well established phenomena, as early as 1971 [17,18], namely the restricted rotations about the C(*s*-triazine)-N(exocyclic) partial double bonds [19-26] governing, overall, the stereo-dynamism of these structures.

Consequently, the aim of the present work is to describe the clean and efficient access to new *N*-substituted amino-*s*-triazines, series **I** and **II** (Scheme 1), together with their stereochemistry focused on rotational Ar-N< aspects.

2. Experimental procedure

2.1. General

Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Bruker® AM300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. VT NMR experiments were performed on a Bruker® DMX500 instrument. All NMR spectra were measured in anhydrous commercially available deuterated solvents. The ^{13}C NMR description of compounds exhibiting frozen rotamers at room temperature was made by considering them as one global structure. Multiple δ_C values for the same-labelled position means mixture of rotamers. Some specific abbreviations were used: bd (broad doublet) bdd (broad doublet of doublets, bq (broad quartet), bm (broad multiplet), *p*-NPh (*p*-nitrophenyl).TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 µm, Merck®). All visualisations were realised in UV at 254 nm. IR spectra were performed on a Perkin-Elmer® Paragom FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) were recorded on a Bruker® Esquire Instrument. Specific rotations were measured on a POLAMAT® Karl-Zeiss Jena instrument. Analytical data and synthesis of compounds **D-NH$_2$ (ax)**, **D-NH$_2$ (eq)** [1,9,10,27-30] and **1a-c** [2] we reported elsewhere.

2.2. Procedures

*Typical procedure for the synthesis of compounds **2a-c** and **3a-c**. Preparation of compound **2c** (Scheme 3)*

To anh. K_2CO_3 (1.512 g, 100%, 10.944 mmol) suspended in anh. THF (100 mL), solid 2-amino-2-(hydroxymethyl)propane-1,3-diol (TRIS, 1.325 g, 10.944 mmol) was added with vigorous stirring. The resulting suspension was cooled at -15°C when cyanuric chloride (2.018 g, 10.944 mmol) as clear anh. THF (25 mL) solution was injected rapidly. The reaction mixture was let gently to reach room temperature and was kept as such for additional 24 hrs. with stirring. After this period, TLC monitoring indicated the intermediate 2,4-dichloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-*s*-triazine **1c** as a single spot (acetone: ligroin 2:1, R_f = 0.80). Freshly prepared (4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxane **D-NH$_2$ (ax)** (2.452 g, 100%, 10.944 mmol) and anh. K_2CO_3 (1.512 g, 100%, 10.944 mmol) were added and the reaction mixture was heated at reflux (65°C) for 12 h. (TLC monitoring, toluene : ^{i}PrOH 2:1, R_f = 0.80). When **D-NH$_2$ (ax)** and **1c** were detected in small traces only, the reaction mixture was cooled at room temperature. Minerals were filtered off and well washed with anh. THF. The organic filtrate was evaporated under reduced pressure to dryness to provide 5.222 g crude product. This was purified by column chromatography on silica gel (toluene : ^{i}PrOH 2:1) affording 4.110 g compound **2c** (84% yield with respect to cyanuric chloride).

2-Chloro-6-{[1,3-dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazine **2a** (80%) yellowish powder, mp 107-118°C (column chromatography, toluene : ^{i}PrOH, 2:1). [Found: C 45.98, H 5.11, N 18.80; $C_{17}H_{21}ClN_6O_6$ (440.12) requires: C 46.32, H 4.80, N 19.06%]. R_f 0.86 (66% toluene/^{i}PrOH). IR ν_{max}. (KBr) 3320 (s), 2946 (m), 2867 (m), 1581 (s), 1520 (s), 1411 (m), 1347 (s), 1242 (m), 1175 (s), 1094 (s), 1027 (s), 966 (m), 852 (m), 804 (s), 744 (m), 711 (m), 592 (w) cm^{-1}. ^{1}H NMR (500 MHz,

[D_6]DMSO, 353 K): δ_H 1.12 (3H, s, Me), 3.48-3.57 (4H, m, CH_2OH), 4.03 (1H, d, $^2J_{H,H}$=11.0 Hz, H-6-a, D-NH), 4.14 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-e, D-NH), 4.37 (1H, d, $^3J_{H,H}$=9.0 Hz, H-5-e, D-NH), 4.50 (2H, bs, OH), 5.00 (1H, d, $^2J_{H,H}$=6.0 Hz, H-2-a, D-NH), 5.23 (1H, d, $^2J_{H,H}$=6.0 Hz, H-2-e, D-NH), 5.28 (1H, s, H-4-a, D-NH), 6.41, 6.51 (1H, 2×bs, SER-N*H*), 7.01 (1H, bs, D-N*H*), 7.66 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.14 (2H, d, $^3J_{H,H}$=7.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 18.7, 18.8, 19.0, 19.4 (Me), 49.3, 49.5, 49.8 (C-5, D-NH), 58.8, 59.0 (C-2, SER-NH), 63.4, 63.5, 63.6, 63.7, 63.8 (CH_2-OH), 69.7, 70.1, 70.2, 70.5 (C-6, D-NH), 77.9, 78.2, 78.4, 78.8 (C-4, D-NH), 93.88, 93.94, 94.0, 94.2 (C-2, D-NH), 123.3, 123.5, 123.6, 123.8 (C-2, -6, *p*-NPh), 127.4, 127.5, 127.6, 127.9 (C-3, -5, *p*-NPh), 146.7, 146.76, 146.78 (C-1, *p*-NPh), 147.17, 147.21, 147.24 (C-4, *p*-NPh), 164.9, 165.1, 165.3, 165.4, 165.6 (C-4, -6, *s*-triazine), 167.76, 167.82, 167.9, 168.2 (C-2, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 463.1 [M+Na$^+$] (7.5), 443.1 [M$^+$+2H] (38), 441.3 [M$^+$+H] (100), 315.1 (10). $[\alpha]_D^{25}$=-46 (0.5% DMSO).

2-Chloro-6-{[1-hydroxy-2-(hydroxymethyl)but-2-yl] amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazine **2b** (66%) yellowish powder, mp 97-102°C (column chromatography, toluene : ^{i}PrOH, 2:1). [Found: C 47.35, H 5.25, N 18.79; $C_{18}H_{23}ClN_6O_6$ (454.14) requires: C 47.53, H 5.10, N 18.48%]. R_f 0.83 (66% toluene/^{i}PrOH). IR $\nu_{max.}$ (KBr) 3372 (s), 2972 (m), 2864 (m), 1587 (s), 1521 (s), 1414 (m), 1346 (s), 1242 (m), 1175 (s), 1095 (s), 1028 (s), 966 (m), 852 (m), 804 (m), 745 (w), 711 (m), 582 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 0.72 (3H, t, $^3J_{H,H}$=7.3 Hz, CH_3), 1.70 (2H, bq, $^3J_{H,H}$=7.2 Hz, CH_2-CH_3), 3.50 (2H, d, $^2J_{H,H}$=11.0 Hz, CH_2-OH), 3.59 (2H, bd, $^2J_{H,H}$=8.5 Hz, CH_2OH), 4.02 (1H, d, $^2J_{H,H}$=11.0 Hz, H-6-a, D-NH), 4.14 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-e, D-NH), 4.37 (3H, bs, H-5-e D-NH, OH), 5.00 (1H, d, $^2J_{H,H}$=6.5 Hz, H-2-a, D-NH), 5.23 (1H, d, $^2J_{H,H}$=6.0 Hz, H-2-e, D-NH), 5.28 (1H, s, H-4-a, D-NH), 6.31, 6.43 (1H, 2×bs, SER-N*H*), 7.02 (1H, bs, D-N*H*), 7.65 (2H, d, $^3J_{H,H}$=7.5 Hz, H-2, -6, *p*-NPh), 8.14 (2H, bd, $^3J_{H,H}$=6.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 303 K): δ_C 7.8, 7.9 (CH_3), 22.1, 22.5, 23.0, 23.1 (CH_2-CH_3), 49.3, 49.37, 49.4, 49.9 (C-5, D-NH), 60.9 (C-2, SER-NH), 61.2, 61.3, 61.4, 61.5 (CH_2OH), 70.07, 70.1, 70.2, 70.5 (C-6, D-NH), 78.2, 78.4, 78.5, 78.8 (C-4, D-NH), 93.89, 93.94 (C-2, D-NH), 123.2, 123.3, 123.4, 123.6, (C-2, -6, *p*-NPh), 127.6, 127.7, 127.9, 128.0 (C-3, -5, *p*-NPh), 146.7, 146.8, (C-1, *p*-NPh), 147.1, 147.17, 147.22 (C-4, *p*-NPh), 164.7, 164.99, 165.04, 165.3, 165.4, 165.7 (C-4, -6, *s*-triazine), 167.8 (C-2, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 493.1 [M+K$^+$] (9), 477.1 [M+Na$^+$] (18), 457.1 [M$^+$+2H] (35), 455.1 [M$^+$+H] (100), 438.2 (11), 437.2 (54), 419.2 (41). $[\alpha]_D^{25}$=-34 (0.5% DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazine **2c** (84%) yellowish powder, mp 200-205°C (column chromatography, toluene : ^{i}PrOH, 2:1). [Found: C 45.01, H 4.39, N 18.59; $C_{17}H_{21}ClN_6O_7$ (456.12) requires: C 44.69, H 4.63, N 18.40%]. R_f 0.80 (66% toluene/^{i}PrOH). IR $\nu_{max.}$ (KBr) 3369 (s), 2950 (m), 2865 (m), 1586 (s), 1519 (s), 1418 (m), 1387 (m), 1347 (s), 1243 (m), 1175 (s), 1096 (s), 1026 (s), 967 (m), 852 (w), 804 (m), 743 (m), 711 (m), 593 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 3.66 (6H, bs, CH_2OH), 4.05 (1H, bd, $^2J_{H,H}$=9.5 Hz, H-6-a, D-NH), 4.14 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-e, D-NH), 4.36 (1H, bs, H-5-e, D-NH), 4.36, 4.53 (3H, 2×bs, OH), 5.00 (1H, d, $^2J_{H,H}$=6.0 Hz, H-2-a, D-NH), 5.23 (1H, d, $^2J_{H,H}$=6.0 Hz, H-2-e, D-NH), 5.27 (1H, bs, H-4-a, D-NH), 6.24, 6.30 (1H, 2×bs, SER-N*H*), 7.01 (1H, bs, D-N*H*), 7.65 (2H, d, $^3J_{H,H}$=8.0 Hz, H-2, -6, *p*-NPh), 8.14 (2H, bd, $^3J_{H,H}$=7.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 49.2, 49.3, 49.7 (C-5, D-NH), 59.4, 59.6, 60.1 (C-2, SER-NH), 62.1, 62.3, 62.4 (CH_2OH), 69.9, 70.3 (C-6, D-NH), 78.0, 78.1, 78.6 (C-4, D-NH), 93.8 (C-2, D-NH), 123.2, 123.4 (C-2, -6, *p*-NPh), 127.4, 127.6, 127.7 (C-3, -5, *p*-NPh), 146.6 (C-1, *p*-NPh), 147.1 (C-4, *p*-NPh), 164.9, 165.0, 165.2, 165.4 (C-4, -6, *s*-triazine), 167.6, 167.8 (C-2, *s*-triazine) ppm. MS (CI, isobutane) *m/z* (rel. int. %) 513 [M$^+$ +^{t}BuH-2H] (20), 495 [M+K$^+$] (9), 457 [M$^+$] (100), 421 (10), 225 (11),140(10). $[\alpha]_D^{25}$=-36 (0.5% DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(methyl)prop-2-yl] amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methyl}amino}-s-triazine **3a** (83%) yellow powder, mp 126-134°C (column chromatography, toluene : EtOH, 1:5). [Found: C 47.95, H 5.51, N 19.39; $C_{20}H_{28}ClN_7O_6$ (497.18) requires: C 48.24, H 5.67, N 19.69%]. R_f 0.80 (17% toluene/EtOH). IR $\nu_{max.}$ (KBr) 3382 (s), 3276 (s), 2941 (m), 2878 (m), 1587 (s), 1521 (s), 1462 (m), 1412 (m), 1349 (s), 1153 (m), 1113 (m), 1057 (s), 852 (w), 804 (m), 753 (w), 709 (m), 571 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 1.27 (3H, s, Me), 2.23 (6H, s, NMe_2), 2.88 (1H, dd as t, $^3J_{H,H}$=3.0 Hz, H-5-e, D-NH), 3.52 (2H, bs, CH_2-NH), 3.60 (4H, bs, CH_2OH), 3.98 (1H, dd, $^3J_{H,H}$=2.0 Hz, $^2J_{H,H}$=12 Hz, H-6-a, D-NH), 4.46 (1H, d, $^2J_{H,H}$=12.0 Hz, H-6-e, D-NH), 4.52 (2H, bs, OH), 5.01 (1H, dd as t, $^3J_{H,H}$=4.3 Hz, H-2-a, D-NH), 5.20 (1H, d, $^3J_{H,H}$=2.0 Hz, H-4-a, D-NH), 6.45, 6.58 (1H, 2×bs, SER-N*H*), 7.48 (1H, bs, CH_2N*H*), 7.66 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.17 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 18.8, 19.0 (CH_3), 43.8 (NMe_2), 44.3, 44,4, 44,8 (CH_2NH), 58.46, 58.51 (C-5,

D-NH), 58.98, 59.04 (C-2, SER-NH), 63.5, 63.6, 63.6, 63.9 (CH_2OH), 64.4, 64.6 (C-6, D-NH), 80.05, 80.12, 80.3 (C-4, D-NH), 99.0, 99.2, 99.5 (C-2, D-NH), 123.3 (C-2, -6, *p*-NPh), 127.1 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 148.8, 148.9 (C-4, *p*-NPh), 165.0, 165.3, 165.6, 165.85, 165.91 (C-4, -6, *s*-triazine), 167.88, 167.93, 168.4 (C-2, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 537.2 [M+K^+] (2), 520.1 [M+Na^+] (3.5), 500.2 [M^++3H], 498.1 [M^++H] (100), 462.2 (7), 273.2 (7), 208.0 (11), 182.2 (17). $[\alpha]_D^{25}$=+147 (0.5% DMSO).

2-Chloro-6-{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methyl}amino}-s-triazine **3b** (42%) yellow powder, mp 110-115°C (column chromatography, Et_2O : EtOH : H_2O, 0.5:8:1). [Found: C 48.98, H 5.81, N 19.39; $C_{21}H_{30}ClN_7O_6$ (511.19) requires: C 49.27, H 5.91, N 19.15%]. R_f 0.73 (5% Et_2O/84% EtOH/H_2O). IR $\nu_{max.}$ (KBr) 3275 (s), 2971 (m), 2881 (m), 1591 (s), 1521 (s), 1464 (m), 1411 (s), 1349 (s), 1154 (m), 1117 (m), 1059 (s), 852 (w), 802 (m), 752 (w), 708 (m), 570 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 0.779, 0.784 (3H, 2×t, $^3J_{H,H}$=7.5 Hz, CH_3), 1.79 (2H, q, $^3J_{H,H}$=7.3 Hz, CH_2CH_3), 2.27 (6H, s, NMe_2), 2.97 (1H, bs, H-5-e, D-NH), 3.51-3.54 (2H, m, CH_2-OH), 3.56 (2H, dd as t, $^3J_{H,H}$=3.0 Hz, CH_2NH), 3.67 (2H, 2×d as t, $^2J_{H,H}$=11.0, 12.5 Hz, CH_2OH), 4.00 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-a, D-NH), 4.49 (1H, d, $^2J_{H,H}$=12.5 Hz, H-6-e, D-NH), 4.53 (2H, bs, OH), 5.01 (1H, dd as t, $^3J_{H,H}$=4.5 Hz, H-2-a, D-NH), 5.24 (1H, bs, H-4-a, D-NH), 6.39, 6.47 (1H, 2×bs, SER-N*H*), 7.50 (1H, bs, CH_2N*H*), 7.67 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.17 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 303 K): δ_C 7.9, 7.96, 8.01, 8.1 (CH_3), 22.2, 22.3, 22.6, 23.0, 23.1 (CH_2-CH_3), 43.8 (NMe_2), 44.2, 44.4, 44.8 (CH_2NH), 58.6 (C-5, D-NH), 60.9, 61.0, 61.1, 61.2, (C-2, SER-NH), 61.46, 61.51, 61.65, 61.71 (CH_2OH), 64.4, 64.6 (C-6, D-NH), 80.0, 80.1, 80.3 (C-4, D-NH), 99.1, 99.3, 99.6 (C-2, D-NH), 123.4 (C-2, -6, *p*-NPh), 127.1 (C-3, -5, *p*-NPh), 146.8 (C-1, *p*-NPh), 148.6, 148.8 (C-4, *p*-NPh), 165.0, 165.2, 165.6, 165.8, 165.9, 166.0, (C-4, -6, *s*-triazine), 167.3, 167.9, 168.3 (C-2, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 515.4 [M^++4H] (8), 514.4 [M^++3H], 512.4 [M^++H] (100), 498.4 (4). $[\alpha]_D^{25}$=+128 (0.5% DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methyl}amino}-s-triazine **3c** (95%) yellow powder, mp 138-140°C (column chromatography, ligroin : acetone, 1:4). [Found: C 47.08, H 5.55, N 19.38; $C_{20}H_{28}ClN_7O_7$ (513.17) requires: C 46.74, H 5.49, N 19.08%]. R_f 0.80 (20% ligroin/acetone). IR $\nu_{max.}$ (KBr) 3369 (s), 2945 (m), 2878 (m), 1583 (s), 1520 (s), 1412 (m), 1348 (s), 1299 (m), 1154 (m), 1113 (m), 1054 (s), 1014 (m), 852 (w), 804 (m), 710 (m), 597 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 2.28 (6H, s, NMe_2), 2.97 (1H, bs, H-5-e, D-NH), 3.53 (2H, s, CH_2-NH), 3.72 (6H, s, CH_2OH), 4.01 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-a, D-NH), 4.42 (3H, bs, OH), 4.49 (1H, d, $^2J_{H,H}$=12.5 Hz, H-6-e, D-NH), 5.03 (1H, bs, H-2-a, D-NH), 5.24 (1H, bs, H-4-a, D-NH), 6.31, 6.40 (1H, 2×bs, SER-N*H*), 7.60 (1H, bs CH_2N*H*), 7.68 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.18 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 43.7 (NMe_2), 44.2, 44.6 (CH_2NH), 58.5 (C-5, D-NH), 59.6, 60.0, 60.2 (C-2, SER-NH), 62.4, 62.5 (CH_2OH), 64.4, 65.3, 67.4 (C-6, D-NH), 80.5 (C-4, D-NH), 99.2 (C-2, D-NH), 123.2 (C-2, -6, *p*-NPh), 126.9 (C-3, -5, *p*-NPh), 146.7 (C-1, -4, *p*-NPh), 165.2, 165.7 (C-4, -6, *s*-triazine), 167.7, 168.2 (C-2, *s*-triazine) ppm. MS (CI, isobutane), *m/z* (rel. int. %) 514 [M^++H] (25) 278 (5), 178 (100), 140 (18), 116(11), 104 (21), 87 (18). $[\alpha]_D^{25}$=+157 (0.5% DMSO).

Typical procedure for the synthesis of compounds ***4a-c*** *and* ***5a-c****. Preparation of compound* ***4c*** *(Scheme 3)*

At room temperature and with vigorous stirring, anh. K_2CO_3 (0.604 g, 4.377 mmol) was suspended in a solution obtained by dissolving anh. piperazine (1.504 g, 17.508 mmol) in anh. THF (125 mL). To this suspension, chlorodiamino-*s*-triazine **2c** (2.000 g, 4.377 mmol) was added portionwise (5 equal portions, 0.400 g **2c** / portion, each 2 h.). After each addition and within 2 hours, TLC monitoring indicated the completion of the reaction as follows: total consumption of **2c** (toluene : ^{i}PrOH = 2:1, R_f = 0.8, visualisation in UV 254 nm) and formation of **4c** (EtOH : aq. NH_3 25% = 9:1, R_f = 0.76, double visualisation: UV 254 nm then I_2 bath). After addition, the reaction mixture was stirred at room temperature for 24 hrs. Minerals were filtered off and well-washed with anh. THF. The combined THF solution was evaporated under reduced pressure to yield 2.900 g crude material which was separated by column chromatography on silica gel (EtOH : aq. NH_3 25% = 9:1, R_f = 0.76, double visualisation: UV 254 nm then I_2 bath). The isolated **4c**, 2.267 g was taken with anh. THF (2 mL) then diethyl ether was added and the resulting fine yellow suspension was stirred at room temperature for 1 hr. After cooling at -20°C for 12 h, filtering off, washing with could diethyl ether and drying, 1.910 g pure **4c** was obtained (86% yield with respect to **2c**).

1-{6-{[1,3-Dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazin-2-yl}-piperazine **4a** (80%) yellowish powder, mp 123-133°C (column chromatography, EtOH : aq. NH_3 25% 9:1). [Found: C 51.55, H 5.80, N 23.03; $C_{21}H_{30}N_8O_6$ (490.23) requires: C 51.42, H 6.16, N 22.84%]. R_f 0.77

(90% EtOH/aq. NH_3 25%). IR $\nu_{max.}$ (KBr) 3400 (s), 2922 (m), 2855 (s), 1548(s), 1501 (s), 1444 (s), 1346 (s), 1274 (m), 1174 (m), 1106 (m), 1056 (m), 1027 (m), 875 (w), 852 (w), 810 (m), 744 (w),711 (m), 583 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 363 K): δ_H 1.21 (3H, s, Me), 2.65 (4H, t, $^3J_{H,H}$=5.0 Hz, H-3, -5, Piperazine), 3.47 (2H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 3.48 (4H, t, $^3J_{H,H}$=5.0 Hz, H-2, -6, Piperazine), 3.56 (2H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 4.02 (1H, d, $^2J_{H,H}$=11.0 Hz, H-6-a, D-NH), 4.11 (1H, dd, $^3J_{H,H}$=1.5 Hz, $^2J_{H,H}$= 11.5 Hz, H-6-e, D-NH), 4.41 (1H, d, $^3J_{H,H}$ = 9.0 Hz, H-5-e, D-NH), 4.54 (3H, bs, OH, Pip-N*H*), 5.00 (1H, d, $^2J_{H,H}$=6.5 Hz, H-2-a, D-NH), 5.225 (1H, s, H-4-a, D-NH), 5.230 (1H,d, $^2J_{H,H}$=5.5 Hz, H-2-e, D-NH), 5.43 (1H, s, SER-N*H*), 5.49 (1H, d, $^3J_{H,H}$=9.5 Hz, D-N*H*), 7.62 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, *p*-NPh), 8.11 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 19.2 (Me), 44.2, 44.3 (C-2, -6, Piperazine), 45.8, 45.9, 46.0 (C-3, -5, Piperazine), 48.8, 48.9 (C-5, D-NH), 57.9 (C-2, SER-NH), 64.6, 64.9 (CH_2OH), 70.5, 70.6, 70.8, 71.0 (C-6, D-NH), 78.5, 78.6, 78.9, 79.0 (C-4, D-NH), 93.9, 94.0, 94.1 (C-2, D-NH), 123.2, 123.5 (C-2, -6, *p*-NPh), 127.4, 127.6 (C-3, -5, *p*-NPh), 147.0, 147.1 (C-1, -4, *p*-NPh), 164.17, 164.22, 164.3, 164.5 (C-2, *s*-triazine), 165.3, 165,4 (C-4, -6, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 491.2 [M^++H] (100), 403.2 (22), 208.0 (29). $[\alpha]_D^{25}$=+28 (0.5% DMSO).

1-{6-{[1-Hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazin-2-yl}-piperazine **4b** (84%) yellowish powder, mp 125-130°C (column chromatography, EtOH : aq. NH_3 25% 9:1). [Found: C 51.99, H 6.22, N 21.95; $C_{22}H_{32}N_8O_6$ (504.24) requires: C 52.37, H 6.39, N 22.21%]. R_f 0.66 (90% EtOH/aq. NH_3 25%). IR $\nu_{max.}$ (KBr) 3401 (s), 2966 (m), 2856 (s), 1552 (s), 1500 (s), 1445 (s), 1346 (s), 1174 (m), 1106 (m), 1061 (m), 1026 (m), 873 (w), 852 (w), 809 (m), 744 (w), 710 (w), 583 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 363 K): δ_H 0.74 (3H, t, $^3J_{H,H}$ = 7.3 Hz, CH_3), 1.73, 1.74 (2H, 2×q, $^3J_{H,H}$=7.5 Hz, CH_2CH$_3$), 2.69 (4H, t, $^3J_{H,H}$=5.0 Hz, H-3, -5, Piperazine), 3.49-3.51 (6H, m, CH_2OH, H-2, -6, Piperazine), 3.56 (2H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 4.02 (1H, d, $^2J_{H,H}$=11.5 Hz, H-6-a, D-NH), 4.12 (1H, dd, $^3J_{H,H}$=1.5 Hz, $^2J_{H,H}$= 11.5 Hz, H-6-e, D-NH), 4.41 (1H, d, $^3J_{H,H}$ = 9.0 Hz, H-5-e, D-NH), 4.54 (3H, bs, OH, Pip-N*H*), 5.00 (1H, d, $^2J_{H,H}$=6.5 Hz, H-2-a, D-NH), 5.23 (1H, d, $^2J_{H,H}$=5.5 Hz, H-2-e, D-NH), 5.24 (1H, s, H-4a, D-NH), 5.35 (1H, s SER-N*H*), 5.52 (1H, d, $^3J_{H,H}$=9.5 Hz, D-N*H*), 7.62 (2H, d, $^3J_{H,H}$=8.0 Hz, H-2, -6, *p*-NPh), 8.10 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 8.1 (CH_3), 23.4, 23.46, 23.54 (CH_2CH$_3$), 43.5, 44.0 (C-2, -6, Piperazine), 45.45, 45.55, 45.64, 45.7 (C-3, -5, Piperazine), 48.8, 48,9 (C-5, D-NH), 60.2 (C-2, SER-NH), 62.5, 62.9 (CH_2OH), 70.5, 70,6 70.8, 70.9 (C-6, D-NH), 78.5, 78.95, 79.04 (C-4, D-NH), 93.9, 94.0 94.1 (C-2, D-NH), 123.2, 123.5 (C-2, -6, *p*-NPh), 127.3, 127.6 (C-3, -5, *p*-NPh), 147.0, 147.1 (C-1, -4, *p*-NPh), 164.5 (C-2, *s*-triazine), 165.4, 165.6 (C-4, -6, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 505.3 [M^++H] (100), 403.2 (25), 224.0 (12), 208.0 (37). $[\alpha]_D^{25}$=+42 (0.5% DMSO).

1-{6-{[1,3-Dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(4S,5S)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-s-triazin-2-yl}-piperazine **4c** (86%) yellowish powder, mp 146-157°C (column chromatography, EtOH : aq. NH_3 25% 9:1). [Found: C 50.11, H 5.88, N 21.90; $C_{21}H_{30}N_8O_7$ (506.22) requires: C 49.80, H 5.97, N 22.12%]. R_f 0.71 (90% EtOH/aq. NH_3 25%). IR $\nu_{max.}$ (KBr) 3392 (m), 2943 (m), 2856 (m), 1549 (s), 1504 (s), 1446 (m), 1346 (s), 1273 (m), 1174 (m), 1105 (m), 1025 (m), 872 (w), 852 (w), 809 (m), 744 (w), 711 (w), 584 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 2.65 (3H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5, Piperazine), 2.68 (1H, s, Pip-NH), 3.46 (4H, t, $^3J_{H,H}$=5.0 Hz, H-2, -6, Piperazine), 3.30 (3H, bs, OH), 3.62 (6H, s, CH_2OH), 4.02 (1H, d, $^2J_{H,H}$=11.0 Hz, H-6-a, D-NH), 4.11 (1H, $^2J_{H,H}$=11.0 Hz, H-6-e, D-NH), 4.40 (1H, bd, $^3J_{H,H}$= 7.5 Hz, H-5-e, D-NH), 5.00 (1H, d, $^2J_{H,H}$=6.5 Hz, H-2-a, D-NH), 5.22 (1H, s, H-4-a, D-NH), 5.23 (1H, d, $^2J_{H,H}$=5.5 Hz, H-2-e, D-NH), 5.43 (1H, s, SER-N*H*), 5.61 (1H, d, $^3J_{H,H}$=9.5 Hz, D-N*H*), 7.63 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, *p*-NPh), 8.12 (2H, d, $^3J_{H,H}$=8.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}QC NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 43.9 (2C, C-2, -6, Piperazine), 45.4 (2C, C-3, -5, Piperazine), 48.8 (1C, C-5, D-NH), 61.0, 61.3 (4C, C-2, CH_2OH, SER-NH), 70.5, 70.7 (1C, C-6, D-NH), 78.4, 78,8 (1C, C-4, D-NH), 93.9 (1C, C-2, D-NH), 123,1, 123,3 (2C, C-2, -6, *p*-NPh), 127.1, 127.4 (2C, C-3, -5, *p*-NPh), 146.9 (2C, C-1, -4, *p*-NPh), 164.2 (1C, C-2, *s*-triazine), 165.0, 165.2, 165.4, 165.5 (2C, C-4, -6, *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane), *m/z* (rel. int. %) 563 [M^++/BuH-2 H] (9), 507 [M^++H] (100), 489 (10), 477 (10), 404 (10),282 (5), 225 (10), 115 (8), 104 (20), 87 (75). $[\alpha]_D^{25}$=+24 (0.5% DMSO).

1-{6-{[1,3-Dihydroxy-2-(methyl)prop-2-yl]amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methy}lamino}-s-triazin-2-yl}-piperazine **5a** (71%) yellow powder, mp 118-123°C (column chromatography, EtOH : aq. NH_3 25% 9:1). [Found: C 52.88, H 7.07, N 22.85; $C_{24}H_{37}N_9O_6$ (547.29) requires: C 52.64, H 6.81, N 23.02%]. R_f 0.57 (90% EtOH/aq. NH_3 25%). IR $\nu_{max.}$ (KBr) 3295 (s), 2932 (s), 2860 (s), 1670 (m), 1548 (s), 1516 (s), 1444 (s), 1348 (s), 1296 (m), 1151 (m), 1113 (m), 1055 (m), 1016 (m), 852 (m), 809 (m), 710 (m), 668 (w), 572 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 1.27 (3H, s, Me), 2.23 (6H, s, NMe_2), 2.69 (4H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5, Piperazine), 2.86 (1H, dd as t, $^3J_{H,H}$=2.8 Hz, H-5-e, D-NH), 3.496

(2H, dd as t, $^3J_{H,H}$=4.5 Hz, CH_2NH), 3.504 (2H, d, $^2J_{H,H}$=10.0 Hz, CH_2OH), 3.58 (4H, t, $^3J_{H,H}$=5.3 Hz, H-2, -6, Piperazine), 3.60 (2H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 3.96 (1H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a, D-NH), 4.46 (1H, d, $^2J_{H,H}$=12.0 Hz, H-6-e, D-NH), 4.66 (3H, bs, OH, Pip-NH), 4.99 (1H, dd as t, $^3J_{H,H}$=4.8 Hz, H-2-a, D-NH), 5.18 (1H, d, $^3J_{H,H}$=3.5 Hz, H-4-a, D-NH), 5.55 (1H, s SER-N*H*), 6.27 (1H, bdd as bt, $^3J_{H,H}$=5.5 Hz CH$_2$N*H*), 7.64 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.16 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO, 298 K): δ_C 19.3 (Me), 43.8 (NMe$_2$), 44.4 (C-2, -6, Piperazine), 45.87, 45.94, 46.03 (C-3, -5, Piperazine, CH$_2$NH), 58.0 (C-2, SER-NH), 58.5, 58.6 (C-5, D-NH), 64.4, 64.5, 64.6 (CH$_2$OH), 64.88, 64.92, 65.3 (C-6, D-NH), 80.1, 80.2 (C-4, D-NH), 99.8, 99.9 (C-2, D-NH), 123.19, 123.24 (C-2, -6, *p*-NPh), 127.0 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 148.9 (C-4, *p*-NPh), 164.7 (C-2, *s*-triazine), 165.9 (C-4, -6, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. Int. %) 548.3 [M$^+$+H] (100), 543.3 (8), 295.2 (10), 217.1 (15), 154.1 (10), 120.1 (3). $[\alpha]_D^{25}$= +145 (0.5% DMSO).

1-{6-{[1-Hydroxy-2-(hydroxymethyl)but-2-yl] amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methyl}amino}-s-tri-azin-2-yl}-piperazine **5b** (67%) yellow powder, mp 112-118°C (column chromatography, EtOH : aq. NH$_3$ 25% 9:1). [Found: C 53.55, H 7.17, N 22.22; $C_{25}H_{39}N_9O_6$ (561.30) requires: C 53.46, H 7.00, N 22.45%]. R_f 0.70 (90% EtOH/aq. NH$_3$ 25%). IR $\nu_{max.}$ (KBr) 3392 (s), 2939 (s), 2856 (s), 1553 (s), 1514 (s), 1446 (s), 1348 (s), 1298 (m), 1151 (m), 1113 (m), 1055 (s), 1011 (m), 852 (m), 710 (m), 573 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ_H 0.79, 0.80 (3H, 2×t, $^3J_{H,H}$ = 7.5 Hz, CH$_3$), 1.80, 1.81 (2H, 2×q, $^3J_{H,H}$=7.5 Hz, CH_2CH$_3$), 2.23 (6H, s, NMe$_2$), 2.70 (4H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5 Piperazine), 2.86 (1H, dd as t, $^3J_{H,H}$=2.3 Hz, H-5-e, D-NH), 3.50 (2H, dd as t, $^3J_{H,H}$=4.5 Hz, CH_2NH), 3.51-3.62 (8H, m, CH_2OH, H-2, -6, Piperazine), 3.96 (1H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a, D-NH), 4.46 (1H, d, $^2J_{H,H}$=12.5 Hz, H-6-e, D-NH), 4.68 (3H, bs, OH, Pip-N*H*), 4.99 (1H, dd as t, $^3J_{H,H}$ = 4.8 Hz, H-2-a, D-NH), 5.18 (1H, d, $^3J_{H,H}$=3.0 Hz, H-4-a, D-NH), 5.46 (1H, s SER-N*H*), 6.29 (1H, bdd as bt, $^3J_{H,H}$=5.5 Hz, CH$_2$N*H*), 7.64 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.16 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO, 298 K): δ_C 8.3 (CH$_3$), 23.5, 23.6 (CH_2CH$_3$), 43.8 (NMe$_2$), 44.3 (C-2, -6, Piperazine), 45.8, (C-3, -5, Piperazine, CH$_2$NH), 58.6 (C-5, D-NH), 60.4 (C-2, SER-NH), 62.8, 63.4 (C-6, D-NH), 64.5 (CH$_2$OH), 80.1, 80.3 (C-4, D-NH), 99.8, 100.1 (C-2, D-NH), 123.2 (C-2, -6, *p*-NPh), 127.0 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 148.93, 148.95 (C-4, *p*-NPh), 164.7 (C-2, *s*-triazine), 165.9, 166.0 (C-4, -6, *s*-triazine) ppm. MS (ESI+), *m/z* (rel. Int. %) 562.3 [M$^+$+H] (100), 548.3 (10), 302.2 (15), 281.7 (25), 208.0 (13), 143.1 (7). $[\alpha]_D^{25}$=+136 (0.5% DMSO).

1-{6-{[1,3-Dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{{[(2R,4S,5S)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methyl}amino}-s-triazin-2-yl}-piperazine ***5c*** (81%) yellow powder, mp 140-145°C (column chromatography, EtOH : aq. NH3 25% 9:1). [Found: C 50.98, H 6.77, N 22.55; $C_{24}H_{37}N_9O_7$ (563.28) requires: C 51.15, H 6.62, N 22.37%]. R_f 0.57 (90% EtOH/aq. NH$_3$ 25%). IR $\nu_{max.}$ (KBr) 3298 (s), 2940 (s), 2858 (s), 1551 (s), 1515 (s), 1446 (s), 1347 (s), 1297 (m), 1151 (m), 1112 (m), 1054 (m), 1015 (m), 852 (m), 809 (m), 710 (w), 578 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ_H 2.23 (6H, s, NMe$_2$), 2.69 (4H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5, Piperazine), 2.86 (1H, dd as t, $^3J_{H,H}$=2.8 Hz, H-5-e, D-NH), 3.30 (1H, bs, Pip-NH), 3.50 (2H, dd as t, $^3J_{H,H}$=4.8 Hz, CH_2NH), 3.57 (4H, t, $^3J_{H,H}$= 4.3 Hz, H-2, -6, Piperazine), 3.66 (6H, s, CH_2OH), 3.97 (1H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a, D-NH), 4.46 (1H, d, $^2J_{H,H}$=12.5 Hz, H-6-e, D-NH), 4.65 (3H, bs, OH), 5.00 (1H, dd as t, $^3J_{H,H}$=4.5 Hz, H-2-a, D-NH), 5.19 (1H, d, $^3J_{H,H}$=3.0 Hz, H-4-a, D-NH), 5.53 (1H, s, SER-N*H*), 6.38 (1H, bs, CH$_2$N*H*), 7.64 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, *p*-NPh), 8.17 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D6]DMSO, 298 K): δ_C 43.7 (NMe$_2$), 44.3 (C-2, -6, Piperazine), 45.8, 46.1, 46.3 (C-3, -5, Piperazine, CH$_2$NH), 58.4 (C-5, D-NH), 61.3, 61.4 (C-2, SER-NH), 64.3 (CH$_2$OH), 65.3 (C-6, D-NH), 80.0 (C-4, D-NH), 99.6 (C-2, D-NH), 123.1 (C-2, -6, *p*-NPh), 126.9 (C-3, -5, *p*-NPh), 146.5 (C-1, *p*-NPh), 148.8 (C-4, *p*-NPh), 164.4 (C-2, *s*-triazine), 165.8 (C-4, -6, *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane), m/z (rel. Int. %) 620 [M$^+$+^{t}BuH-2H] (5),564 [M$^+$+1] (65), 449 (28), 380 (55), 300 (10), 282 (15), 221 (5), 178 (100), 165 (25), 148 (10), 104 (45), 87 (35). $[\alpha]_D^{25}$=+137 (0.5% DMSO).

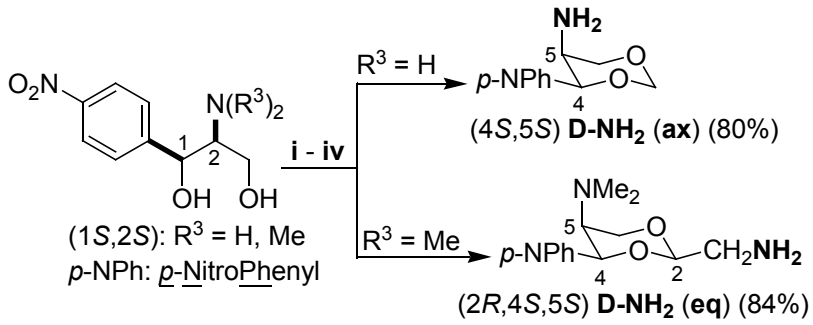
3. Results and discussion

3.1. Synthesis

Our chemistry is depicted in Schemes 2 and 3.

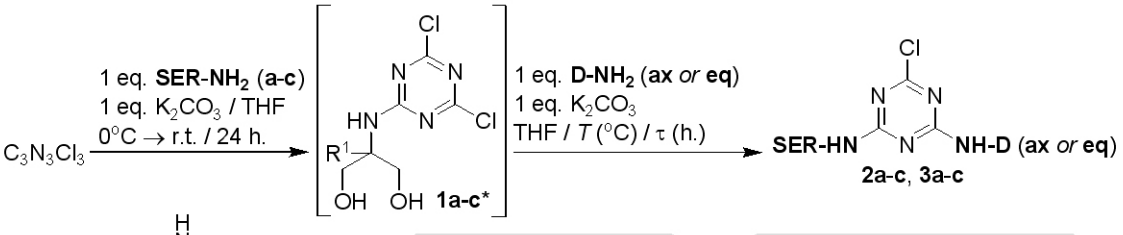
Enantiopure amino-1,3-dioxanes **D-NH$_2$** (**ax** or **eq**) were routinely prepared (Scheme 2) by our diastereospecific "sulphuric acetalisation" method [1,9,10,27-30] applied to the corresponding (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diols ("*Threo-p-nitrophenylserinols*" [29]).

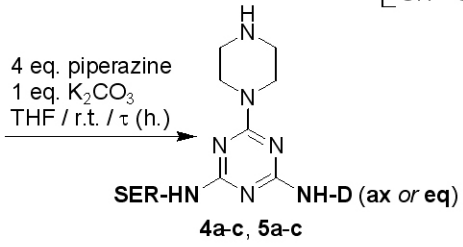
Next, the optimised protocol directed to chlorodiamino-*s*-triazines **2** and **3** consisted of using C-2-substituted serinols, **SER-NH$_2$** (**a**-**c**) (Scheme 1), as the first amino-nucleophile against cyanuric chloride, then **D-NH$_2$** (**ax**), in a one-pot synthesis. Indeed, in series **2**, the inverted employ of serinolic reagents



Key **i)** 10 eq. H_2SO_4 (c 96%) / 0°C; **ii)** 1 eq. H_2CO / 0°C [® **D-NH$_2$ (ax)**] *or* 1 eq. H_2N-CH_2-$CH(OR^4)$ (R^4 = Me, Et) [® **D-NH$_2$ (eq)**]; **iii)** 0°C ® r.t. / 24 h.; **iv)** aq. NH_3 (c 25%) / 0°C / pH=9

Scheme 2. Synthesis of *p*-nitrophenylserinols based amino-1,3-dioxanes as „*closed-chain*" unit by „sulphuric acetalisation".





axial anchorage of **D** (**ax**)

No.	*T* (°C), τ (h.)	yield (%)
2a	65, 16	80
2b	65, 22	66
2c	65, 12	84
4a	r.t., 24**	80
4b	r.t., 24	84
4c	r.t., 24	86

equatorial anchorage of **D** (**eq**)

No.	*T* (°C), τ (h.)	yield (%)
3a	-10 → r.t., 24; 65, 14	83
3b	-10 → r.t., 24; 65, 16	42
3c	-10 → r.t., 24; 65, 12	95
5a	r.t., 24**	71
5b	r.t., 24	67
5c	r.t., 24	81

*not isolaled; for the full characterisation of these intermediates, see [2]
5×0.2 eq. **2a-c *or* **3a-c** added portionwise each 2 h; the completion of reaction required additional 14 h.

Scheme 3. Synthesis of targeted *N*-substituted amino-s-triazines.

produced lower yields, *e.g.*, in the case of **2c** from 84% (Scheme 3) to 55%. We note that, targeting series **3**, previous findings of us [1] evidenced, unsurprisingly [31-39], the (non)-selective interaction between equimolar amounts of cyanuric chloride and amino-1,3-dioxane **D-NH$_2$ (eq)** as side oligomerisations and C-5-*N*-demethylation, both with low yield. Therefore, the single option we had was employed, yet again, of **SER-NH$_2$** (**a-c**) as the first nucleophiles, followed by **D-NH$_2$ (eq)**.

In the last context, one can observe the milder conditions in the synthesis of compounds **3a-c** *vs.* **2a-c**. They were inspired mainly from Kolesinska's *et al*. recent report [39] demonstrating the high reactivity, even at room temperature, of some less π-deficient than **1a-c** *N*-substituted 2,4-dichloro-6-amino-*s*-triazines with respect to elaborated tertiary amines. In our case, however, the clean selective evolution of the subsequent aminations, **1a-c** → **3a-c**, we explained by the sterically crowded environment of the axial C-5 dimethylamino group in **D-NH$_2$ (eq)**.

The chemoselective attachment of the third nucleophile was accomplished based on our previously reported procedure [2,3], the portionwise addition, at room temperature, of chlorodiamino-*s*-triazines **2a-c** and **3a-c** to a four fold molar amount of piperazine. Melamines **4a-c** and **5a-c** were purified by column chromatography on partially deactivated silica gel. No dimeric by products were detected, presumably because of the transannular effect of piperazine favouring its mono-*N*-substitution, as previously noticed by Lai *et al*. [40,41] and independently observed by us [1-3].

Compounds **4a-c** and **5a-c** can be seen as novel building-blocks for further iterative synthesis taking into account the presence of the remaining free NH functionality of piperazine, a widely recognised linker in melamines' dendritic synthesis [2,3,12,40-51].

3.2. Rotational stereochemistry phenomena

Starting from the well-known herbicide ATRAZINE® (2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine) analysis [17,18], the lp_N(exocyclic) → π(deficient *s*-triazine) delocalisation determining restricted rotation about the partial double bonds C(*s*-triazine)-N(exocyclic) thus created, is an already well documented feature in amino-*s*-triazines. The assignment of the resulted rotamers is a quite difficult task, both in solution and in solid state [19-26]. Besides investigations by NMR on the tandem time-temperature scales, computational methods [19,25] including DFT approaches by us [1-3,52] are also of interest. Usually, preceding studies focused on *N*-(un)symmetrically substituted melamines by means of (VT) NMR at low temperature [22-26]. Apart from ATRAZINE®, minor attention was paid to *N*,*N*'-substituted-2-chloro-4,6-diamino-*s*-triazines [19-22]. To our knowledge, it was limited to the dynamic behaviour, upon heating, of symmetric 2-chloro-4,6-bis(*N*,*N*-dialkylamino) derivatives.

Therefore, some characteristics defining our *N*-unsymmetrically substituted amino-*s*-triazines are mandatory.

The serinolic "*open-chain*" *N*-ligands **SER** (**a**-**c**), containing a variable number of geminal hydroxymethyl groups, were *a priori* seen as the most OH solvated motifs of the molecules while the "*closed-chain*" *N*-ligands, **D** (**ax** *or* **eq**), had anancomeric 1,3-dioxanic skeletons due to the overwhelmingly one-sided conformational equilibria, by the adoption of an equatorial position by the C-4-*p*-nitrophenyl group [53,54]. Moreover, the anchorage of our "sugar like" **D** *N*-ligands to amino-*s*-triazine was different, axial in **2a**-**c** and **4a**-**c** but equatorial in **3a**-**c** and **5a**-**c**.

Since we normally expected their rotational behaviour to be dependent on the π-deficiency of *s*-triazine core, our exploration followed its decreasing nature, from chlorodiamino-derivatives **2**- and **3a**-**c** to melamines **4**- and **5a**-**c**.

3.2.1. N,N'-unsymmetrically substituted 2-chloro-4,6-diamino-s-triazines

3.2.1.1. Analysis of frozen equilibria: assignment of rotamers

As expected, at room temperature, each compound in series **2** and **3** was a non-statistic mixture of blocked rotational diastereomers about the partial double bonds C(-4, -6, *s*-triazine)-N(exocyclic) (Scheme 4). Since the latter were two axes of diastereomerism [1,2], a topologically idealised model predicted a frozen four-component global equilibrium. Each of them can be generated by a single rotation / local equilibrium and originates from two independent pathways. We previously detailed the utility of this "step by step approach" [1-3].

The relevant ^{1}H NMR data associating this stereodynamism is listed in Tables 1 and 2.

On ^{1}H 500 MHz timescale, rotameric species were displayed accurately by the **SER**-N***H*** signals of compounds **2a**-**c** (all four species) and, in part, by **3a**-**c** (three species). On ^{13}C 125 MHz timescale, the four stereoisomers were more convincing by detection of four sets of peaks for almost all relevant *C*-environments (see Experimental procedure).

The mixtures contents were calculated and correlated based on ^{1}H integrals of the best separated "amide like" protons **D**-N***H*** (H-α, -β, -γ and -ε) and **SER**-N***H*** (H-α', -β', -γ' and -ε') (Supplementary Fig. 1).

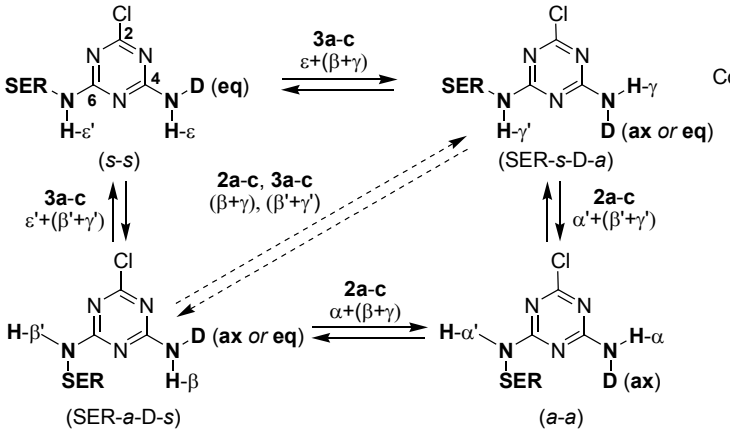
The individual assignment started from the 2D-^{1}H,^{1}H-NOESY chart of compound **2a** (Scheme 5; Supplementary Fig. 2) exhibiting two dipolar interactions between the proton **SER**-N***H*** (6.46 ppm, signal H-γ') and those of *p*-nitrophenyl ring of the axially anchored **D** (**ax**) counterpart, hence a "*trans*" relationship between the *N*,*N*'-ligands in a (SER-*s*-D-*a*) (16.5%) arrangement (Scheme 4). Then, the alternative "*trans*" orientation of the *N*,*N*'-ligands of **2a**, (SER-*a*-D-*s*), was deduced reasonably, since its incidence was comparable (19.5%, Scheme 4).

The major rotamer **2a** (*a*-*a*) was preliminarily established by considering the two close **SER**-N***H*** δ_{NH} values of protons H-α' and H-β', in their *anti* local environment: 6.74 ppm in **2a** (SER-***a***-D-*s*, H-β') and 6.86 ppm in **2a** (***a***-*a*, H-α') (Table 1). If so, *mutatis-mutandis*, in the *syn* location, rotamers **2a** (SER-***s***-D-*a*) and **2a** (***s***-*s*), δ_{NH} of the same type of protons were also much related, 6.46 ppm (signal H-γ') and 6.41 ppm (signal H-ε') respectively.

Although compound **2a** was the single one in both series **2** and **3** for which the nature of rotamerism could be deduced from a NOESY Experiment, our investigation was not quite in a *testis unus testis nullus* situation.

Thus, extrapolation of the above result to the entire series **2** disclosed, for the **SER** "*open-chain*" *N*-ligands (signals H-α', -β', -γ', -ε'), the magnitude of their NH chemical shifts being modulated by the strong dipole moment of the bond (C-2, *s*-triazine)-Cl causing deshileding in its local proximity as δ_{NH} (*anti*) > δ_{NH} (*syn*) [55]. This previously deduced, by us, "dipole rule" [1,2,52] did not fit, however, for the δ_{NH} values in the **D**-N***H*** (**ax**) fragment (Table 1).

Therefore, in order to further support these findings and to predict the rotameric occurrence in series **3**, computational methods were performed in the case of compounds **2a** and **3a** (Table 3). Thus, by optimisation of

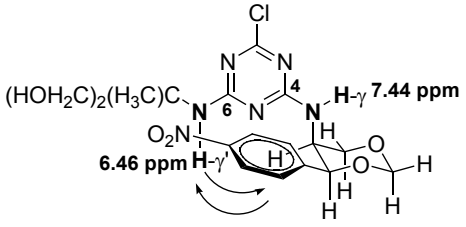


Content of frozen rotamers (%) (298 or 303 K)

	(*a*-*a*)	(SER-*a*-D-*s*)	(SER-*s*-D-*a*)	(*s*-*s*)
Axial anchorage of D (ax) *N*-ligand				
2a	62	19.5	16.5	2
2b	56.5	19.5	16	8
2c	52	23	18	7
Equatorial anchorage of D (eq) *N*-ligand				
3a	-	19	19	62
3b	-	15	18	67
3c	-	22	21	57

Key **i)** the chlorine atom and **SER** or **D** *N*-ligand are used as reference for *a* (*anti*) or *s* (*syn*) stereochemical descriptors.
ii) **NH**-$\alpha^{(\prime)}$, -$\beta^{(\prime)}$, -$\gamma^{(\prime)}$, -$\varepsilon^{(\prime)}$: the best ^{1}H NMR separated signals, used for calculation of rotameric content and kinetic parameters (Tables 1, 2, 4 and 5).

Scheme 4. Rotational diastereomers of *N,N'*-unsymmetrically substituted 2-chloro-4,6-diamino-*s*-triazines **2a-c** and **3a-c**, their abundances and sequential interconversion.



2a (D-*a*-SER-*s*)

Scheme 5. 2D-^{1}H,^{1}H-NOESY result for compound **2a** (on 500 MHz timescale in [D_6]DMSO).

their rotational diastereomers (*a*-*a*) and (*s*-*s*) at B3LYP/6-311++G** level of theory and taking into account the effect of solvent (DMSO), we found that:

i) In compounds **2a**-**c**, in fully agreement with ^{1}H NMR data, the frozen arrangement (*a*-*a*) was major whereas rotamers **2a**-**c** (*s*-*s*) should be the minor ones.

ii) In contrast, in series **3**, if the 1,3-dioxanic *N*-ligand was equatorially anchored to amino-*s*-triazine, rotamers **3a**-**c** (*s*-*s*) were, this time, the prevailing species.

iii) Bond orders C(*s*-triazine)-N[**D** (**ax**) or (**eq**), **SER** (**a**-**c**)] being almost identical (1.22 – 1.25), the electronic factors we saw responsible neither for the opposite dominant incidence of certain rotamer, **2a**-**c** (*a*-*a*) against **3a**-**c** (*s*-*s*), nor for their subsequent rotational activation.

Regardless of the type of **D** *N*-ligand linkage (Tables 1 and 2), in each series, the most polar stereoisomers, hence the highest solvated, were the major ones, displaying the most deshielded indicative protons, **SER-N*H*** and **D-N*H***, as well. Surprisingly, in spite of conflicting dominance of the major type of rotamer, **2** (*a*-*a*) *vs.* **3** (*s*-*s*), overall, the rotameric content and hierarchy were similar in the two series (Scheme 4), including the "dipole rule" in the **SER-N*H*** δ_{NH} sequence.

Temperature Gradients (TG) applied to ^{1}H NMR NH signals provided additional information.

As recently recommended by Simanek *et al.* [16], even if this parameter is usually applied to peptides and proteins [56], it is generally accepted and indicative that if the NH TG of our "amide like" protons is more negative than -4 ppb/K in a hydrogen bond acceptor solvent [22,56], such as [D_6]DMSO, the NH group was exposed to solvent and not involved in intramolecular hydrogen bonds. Conversely, a TG less negative than -4 ppb K^{-1} indicates the NH protons being, at room temperature, involved in intramolecular hydrogen bonding (see example of TGs calculation in SM-3).

If so, in complete accord with DFT calculation, the major species **2** (*a*-*a*) and **3** (*s*-*s*) were the most **D-** (or **SER-N**)***H***…O=SMe_2 solvated (Tables 1 and 2). On the whole, TG **D-N*H*** (**ax**) values were slightly greater than TG **D-N*H*** (**eq**). In contrast, TGs of **SER-N*H*** (**a**-**c**) were much less negative than TGs of **D-N*H*** (**ax** or **eq**). We explained this situation by the intramolecular ability of geminal hydroxymethyl groups to partially associate the adjacent NH, *i.e.*, >C(CH_2OH)$_n$…HN< (n = 2, 3). Indeed, TRIS as **SER-N*H*** (**c**, n = 3) derivatives **2c** and **3c** exhibited the less negative TGs.

3.2.1.2. Analysis of dynamic equilibria: steric factors against solvation effects

When submitted to progressively increased temperatures up to 80°C, our molecules reached complete mobility about the bonds C(*s*-triazine)-N[**D** (**ax**) or (**eq**)] only. As shown in Fig. 1 and Tables 1 and 2 (see also Supplementary Figs. 3 and 4), the typical ^{1}H NMR final appearance in both series was consistent with a slow freely rotational motion of the **D** (**ax** or or **eq**) *N*-ligand (one NH broad singlet) meanwhile, for the **SER** *N*-ligand,

Table 1. Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)-N(exocyclic) bonds in *N,N'*-unsymmetrically substituted chlorodiamino-*s*-triazines **2a-c** (on 500 MHz timescale in [D_6]DMSO).

No.	*T* (K)	*N*-Ligand data	Rotamer			
			(*a-a*)	(SER-*a*-D-*s*)	(SER-*s*-D-*a*)	(*s-s*)
			Discriminating δ_{NH} (ppm) values and multiplicity			
			H-α H-α'	H-β H-β'	H-γ H-γ'	H-ε H-ε
			Temperature Gradients (TG) as ($\Delta\delta_{NH}$ / ΔT) × 10^3 (ppb/K)[a]			
2a	298	δ_{NH} D-N*H* (ax)	7.62 (d)[b]	7.52 (d)	7.44 (d)	-[c]
		δ_{NH} SER-N*H* (a)	6.86 (s)	6.74 (s)	6.46 (s)	6.41 (bs)
	353		δ_{NH} D-N*H* (ax): 7.01 (bs); SER-N*H* (a): 6.51 (bs)[d], 6.41 (bs)[e]			
		TG D-N*H* (ax)	-11.1	-9.3	-7.8	-
		TG SER-N*H* (a)	-6.4	-6.0	-0.9	0
2b	303	δ_{NH} D-N*H* (ax)	7.62 (d)	7.52 (d)	7.46 (d)	-
		δ_{NH} SER-N*H* (b)	6.77 (s)	6.64 (s)	6.34 (s)	6.33 (bs)
	353		δ_{NH} D-N*H* (ax): 7.02 (bs); SER-N*H* (b): 6.43 (bs)[d], 6.31 (bs)[e]			
		TG D-N*H* (ax)	-12.0	-10.0	-8.8	-
		TG SER-N*H* (b)	-6.8	-6.6	-0.6	-0.4
2c	303	δ_{NH} D-N*H* (ax)		7.53, 7.52, 7.49[d]		
		δ_{NH} SER-N*H* (c)	6.57 (s)	6.50 (s)	6.27 (s)	6.21 (bs)
	353		δ_{NH} D-N*H* (ax): 7.01 (bs); SER-N*H* (c) : 6.30 (bs)[d], 6.24 (bs)[e]			
		TG D-N*H* (ax)	-	-	-	-
		TG SER-N*H* (c)	-5.4	-5.2	-0.6	-

[a]$\Delta\delta_{NH} = [\delta_{NH}(T) - \delta_{NH}(T_{r.t.})] < 0$; $\Delta T = (T - T_{r.t.}) > 0$ (K) where T = 353 K and $T_{r.t.}$ is the room temperature, 298 or 303 K. [b]Doublet with a typical $^3J_{H,H}$(ax-NH-H-5-e) = 9.0 – 10.0 Hz in D (ax) N-ligand. [c]Rotamers not found on the NH zone of the spectra but detected on ^{13}C NMR time scales (see Experimental Procedure); in series 2a-c the corresponding abundance was adopted from the SER-NH signal H-ε' (Scheme 4). [d]Not assignable as overlapped signals. [d]Signal considered for calculation of SER-NH TG of rotamer (a-a) (see SM-3). [e]Signal used for calculation of SER-NH TG of rotamers (SER-a-D-s) and (SER-s-D-a) (see SM-3).

Table 2. Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)-N(exocyclic) bonds in N,N'-unsymmetrically substituted chlorodiamino-*s*-triazines **3a-c** (on 500 MHz timescale in [D_6]DMSO).

No.	*T* (K)	*N*-Ligand data	Rotamer			
			(*a-a*)	(SER-*a*-D-*s*)	(SER-*s*-D-*a*)	(*s-s*)
			Discriminating δ_{NH} (ppm) values and multiplicity			
			H-α H-α'	H-β H-β'	H-γ H-γ'	H-ε H-ε'
			Temperature Gradients (TG) as ($\Delta\delta_{NH}$ / ΔT) × 10^3 (ppb/K)[a]			
3a	298	δ_{NH} D-N*H* (eq)	-[b]	7.89 (dd as t)[c]	7.91 (dd as t)	8.03 (dd as t)
		δ_{NH} SER-N*H* (a)	-	6.80 (s)	6.82 (s)	6.92 (s)
	353		δ_{NH} D-N*H* (eq): 7.48 (bs); SER-N*H* (a): 6.58 (bs)[d], 6.45 (bs)[e]			
		TG D-N*H* (eq)	-	-7.5	-7.8	-10.0
		TG SER-N*H* (a)	-	-6.4	-6.7	-6.2
3b	298	δ_{NH} D-N*H* (eq)	-	7.88 (dd as t)	7.91 (dd as t)	8.05 (dd as t)
		δ_{NH} SER-N*H* (b)	-	6.71 (s)	6.75 (s)	6.83 (s)
	353		δ_{NH} D-N*H* (eq): 7.50 (bs); SER-N*H* (b): 6.47 (bs)[d], 6.39 (bs)[e]			
		TG D-N*H* (eq)	-	-6.9	-7.5	-10.0
		TG SER-N*H* (b)	-	-5.8	-6.5	-6.5
3c	303	δ_{NH} D-N*H* (eq)	-	7.92 (dd as t)	7.94 (dd as t)	8.01 (dd as t)
		δ_{NH} SER-N*H* (c)	-	6.56 (s)	6.60 (s)	6.64 (s)
	353		δ_{NH} D-N*H* (eq): 7.60 (bs); SER-N*H* (c): 6.40 (bs)[d], 6.31 (bs)[e]			
		TG D-N*H* (eq)	-	-6.4	-6.8	-8.2
		TG SER-N*H* (c)	-	-5.0	-5.8	-4.8

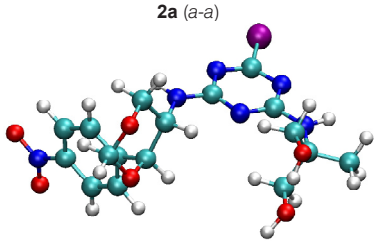
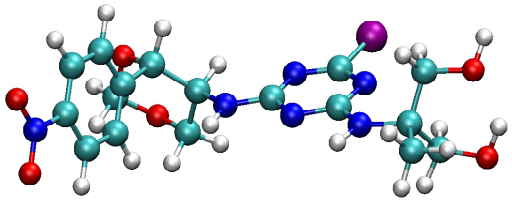
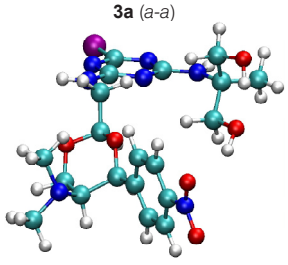
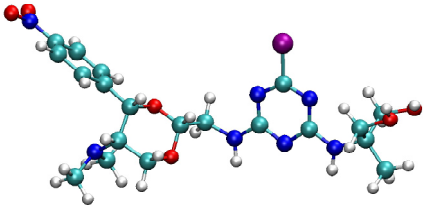
[a]$\Delta\delta_{NH} = [\delta_{NH}(T) - \delta_{NH}(T_{r.t.})] < 0$; $\Delta T = (T - T_{r.t.}) > 0$ (K) where T = 353 K and $T_{r.t.}$ is the room temperature, 298 or 303 K. [b]Rotamers not found on the NH zone of the spectra but detected on ^{13}C NMR time scales (see Experimental Procedure). [c]Doublet of doublets as triplet with typical $^3J_{H,H}$(eq-CH$_2$-NH) = 6.0 – 6.6 Hz in D (eq) N-ligand. [d]Signal considered for calculation of SER-NH TG of rotamer (s-s) (see SM-3). [e]Signal used for calculation of SER-NH TG of rotamers (SER-a-D-s) and (SER-s-D-a) (see SM-3).

its two NH broad singlets were symptomatic for a partial turning "activation", *i.e.*, a slow exchange between two unequally populated sites.

In our attempt to estimate the temperature dependent equilibria in Scheme 4, we had to adapt, like it or not, three simplifying hypotheses:

i) By intercalation of the *s*-triazine ring in between, the two *N,N'*-ligands were "sufficiently remote" for the relevance of a certain NH signal exposed by each of them, **D-N*H*** (**ax** and **eq**, H-α, -β, -γ, -ε) or **SER-N*H*** (H-α', -β', -γ', -ε'), be limited to the rotational behaviour of the unit to that this signal belongs, **D** or **SER**.

Table 3. Bond orders (B.O.), dipole moments μ (D), ZPE corrected relative energies ΔH_{0K} (kJ mol^{-1}) and relative free energies ΔG_{298} (kJ mol^{-1}) of frozen rotamers (*a*-*a*) and (*s*-*s*) of compounds **2a** and **3a**.

B.O.[a] C(4)-N<	B.O. C(6)-N<	D	ΔH_{0K}	ΔG_{298}	B.O. C(4)-N<	B.O. C(6)-N<	D	ΔH_{0K}	ΔG_{298}
2a (*a*-*a*)					**2a** (*s*-*s*)				
									
B3LYP/6-31G* (gas phase)									
-	-	5.27	1.00	0.00	-	-	3.52	0.00	0.63
B3LYP/6-311++G* / CPCM / DMSO[b]									
1.23	1.25	4.84	0.00	0.00	1.22	1.24	2.07	2.93	3.14
3a (*a*-*a*)					**3a** (*s*-*s*)				
									
B3LYP/6-31G* (gas phase)									
-	-	5.10	2.39	4.31	-	-	7.85	0.00	0.00
B3LYP/6-311++G* / CPCM / DMSO									
1.24	1.25	7.81	0.00	1.38	1.24	1.24	11.63	1.38	0.00

[a]Wiberg bond order calculated within the NBO (Natural Bonding Orbital) analysis. [b]The effect of solvent took into account by using the implicit solvent method CPCM (Conductor-like Polarizable Continuum Model) implemented in Gaussian 09.

ii) Since species **2a**-**c** (*s*-*s*) and **3a**-**c** (*a*-*a*) were minor or even not detected on the ^{1}H NMR timescale, we only neglected their content and not their existence.

iii) The consecutive activation of the remaining three equilibria (Scheme 4) was considered disclosed by the succession in which coalescences of ^{1}H NH signals appeared (Supplementary Figs. 3 and 4).

All hereafter kinetic parameters [57,58] were calculated comparatively with the use of Shanan-Atidi algorithm [59], Gutowski-Holm [60] and Eyring Equations [57]. They are collected in Tables 4 and 5 (see also SM-5).

The opening (SER-***s***-D-***a***) ⇆ (SER-***a***-D-***s***) ("*trans*" ⇆ "*trans*") global equilibria (Supplementary Figs. 2 and 3) were the first observed and VT ^{1}H NMR monitored by means of coalescences of the pairs of signals **D-N*H*** (β + γ) and **SER-N*H*** (β' + γ'). They referred to close populated sites, (50 ± 5)% and, since initially detected, we believed that they occurred, most likely, *via* the minor rotamers **2** (*s*-*s*) or **3** (*a*-*a*), to reveal their rather predicted "rotational instability".

In series **2**, as shown by the very different T_C values, ΔT_C (β + γ *vs.* β' + γ') ~ 30 K, the two *N,N'*-ligands were not "synchronised" at all, deblocking about the bond C(*s*-triazine)-N[**D** (**ax**)] occurring first, **2** (*s*-***s***) ⇆ **2** (SER-*s*-D-***a***). We ascertained the result of this early "rotational competition" by the crowded anchorage of the **D** (**ax**), due to the steric repulsion between its two C-4-eq, -5-ax adjacent aromatic rings, determining instability of its ground state (Scheme 5). Accordingly, the corresponding energetic barriers about bond C(*s*-triazine)-N[**D** (**ax**)], $\Delta G^{\neq}_M$ and $\Delta G^{\neq}_m$ (Table 4), were the smallest found in the present study. Next, since the **D** (**ax**) *N*-ligand had already reached rotational mobility, its more as (OH) solvated **SER** (**a**-**c**) partners had also to accommodate the above priority by a delayed start about the bond C(*s*-triazine)-N[**SER** (**a**-**c**)], **2** (***s***-*s*) ⇆ **2** (SER-***a***-D-*s*).

In contrast, in compounds **3a**-**c**, the same "*trans* ⇆ *trans*" double equilibration, (*a*-***a***) ⇆ **3** (SER-*a*-D-***s***) and **3** (***a***-*a*) ⇆ **3** (SER-***s***-D-*a*), became active about at the same time (ΔT_C = 0 – 10 K), *i.e.*, the *N,N'*-ligands formed a rotational tandem.

In series **2**, $\Delta G^{\neq}$ values of **D** (**ax**) *N*-ligand were smaller than those of **D** (**eq**) in series **3**, to confirm the more stable ground state of the latter. On the contrary,

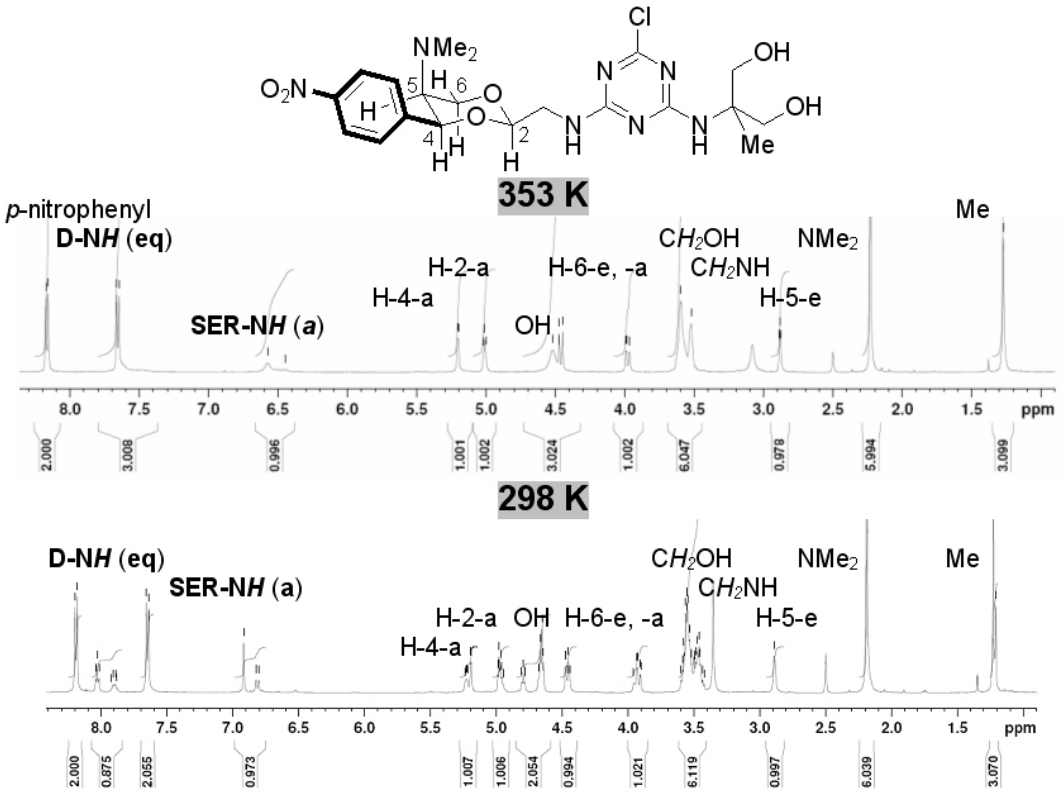


Figure 1. ^{1}H NMR temperature evolution of compound **3a** (on 500 MHz timescale in [D_6]DMSO).

rotational barriers of the **SER** *N*-ligand in **2a-c** were higher with respect to those in **3a-c**, presumably because of a less crowded transition state when the **D** *N*-ligand was equatorially positioned.

Additional heating revealed a second type of equilibration, **2** (*a*-***a***) ⇆ **2** (SER-*a*-D-***s***) and **3** (*s*-***s***) ⇆ (SER-*s*-D-***a***) (Table 5, Supplementary Figs. 2 and 3) seen by us as a partial activation of the most stable rotamers, **2a-c** (*a*-*a*) and **3a-c** (*s*-*s*) respectively. Thus, after the first two coalescences, (β + γ) and (β‘ + γ ‘) (Table 4), a subsequent two were observed, [α + (β + γ)] in series **2** and [ε + (β + γ)] in series **3**. They were consistent with a single rotation, that of the 1,3-dioxane *N*-ligands about the bonds C(*s*-triazine)-N[**D** (**ax**) or (**eq**)] providing final (353 K) broad singlets of protons **D-NH**, indicative for a slow free turning motion located in this part of our *N,N'*-unsymmetrically disubstituted 2-chloro-4,6-diamino-*s*-triazines.

If so, by considering the normal shifting of these final equilibria as **2** (SER-*a*-D-***s***) → **2** (*a*-***a***) but **3** (SER-*s*-D-***a***) → **3** (*s*-***s***) and their consecutive occurrence with respect to the previous "*trans* ⇆ *trans*", a comparison between $\Delta G^{\neq}_m$ (m → M) values (Table 5) we saw of interest. In fact, they revealed, this time, the steric influence of the **SER** *N*-ligands, assisting rotation of **D-NH** (**ax** or **eq**) counterparts. Thus, **D** (**ax**) derivatives **2a** and **2b** had higher $\Delta G^{\neq}_m$ values (2-3 kJ/mol) than **3a-c** to suggest the prevalence of steric factors in the transition states of this local interconversion: compounds **2a** and **2b** had to accommodate a final (*a*-*a*) geometry meanwhile **3a-c**, a less crowded (*s*-*s*).

To conclude, in spite of their opposite construction, it was the most stable rotamers, **2a-c** (*a*-*a*) and **3a-c** (*s*-*s*), which could not be completely activated up to 80°C with respect to the same partial double bond, C(*s*-triazine)-N[**SER** (**a-c**)]. Indeed, equilibria **2** (***a***-*a*) ⇆ **2** (SER-***s***-D-*a*) and **3** (***s***-*s*) ⇆ **3** (SER-***a***-D-*s*), implying rotation of the **SER** (**a-c**) *N*-ligands, were not VT ^{1}H NMR observed. We deduced, once again, that the high OH solvation combined with a significant NH contribution (expressed by TG values, Tables 1 and 2) were both responsible for this **SER** "residual immobility".

3.2.2. N,N',N''-unsymmetrically substituted melamines

3.2.2.1. Rotational (pro)diastereomerism at room temperature

Keeping in mind the above findings, analysis of melamines **4a-c** and **5a-c** screened the same structural features as they appeared according to NMR spectroscopy. Significant ^{1}H NMR data observations are collected in Table 6.

Table 4. Kinetic parameters deduced from VT ^{1}H NMR of compounds **2a-c** and **3a-c** for the "*trans* ⇆ *trans*" global equilibria (SER-***a***-D-***s***) ⇆ (SER-***s***-D-***a***) (see Scheme 4).

No.	Signals considered Relative populations (%)		Kinetic parameters for rotation of					
			amino-1,3-dioxanic group (D-NH) "*Closed-chain*" *N*-ligand			Serinolic group (SER-NH) "*Open-chain*" *N*-ligand		
	SER-*a*-D-*s* ⇆ SER-*s*-D-*a*							
	β' β	γ' γ	T_C (K) (β + γ)[a]	$k_{C\text{-}M}$[b] $k_{C\text{-}m}$[c] (s^{-1})	$\Delta G^{\neq}_M$ $\Delta G^{\neq}_m$ (kJ mol^{-1})	T_C (K) (β' + γ')[a]	$k_{C\text{-}M}$ $k_{C\text{-}m}$ (s^{-1})	$\Delta G^{\neq}_M$ $\Delta G^{\neq}_m$ (kJ mol^{-1})
2a	54	46	323	69.4 88.5	67.93 67.50	353	249.1 292.5	70.75 70.28
2b	55	45	323	48.0 58.6	68.92 68.38	353	249.8 305.4	70.74 70.15
2c	56	44	-	-	-	343	188.3 239.7	69.46 68.77
3a	50	50	318	20.0	70.13	313	22.2	68.71
3b	45.5	54.5	328	21.2 25.4	72.26 71.76	318	31.4 37.6	68.93 68.46
3c	51	49	318	14.5 15.1	70.98 70.87	318	40.3 41.9	68.27 68.17

[a]*Signals providing coalescence (Table 1).* [b]*Kinetic data for the Major rotamer.* [c]*Kinetic data for the minor rotamer*

Table 5. Kinetic parameters deduced from VT ^{1}H NMR of compounds **2a**, **2b** and **3a-c** for rotation of the "*closed-chain*" **D** (**ax** or **eq**) *N*-ligand (see Scheme 4).

No.	Equilibrium Signals considered Relative populations (%)		Kinetic parameters		
	(SER-*a*-D-***s***) ⇆ (*a*-***a***) β α		T_C (K) α + (β + γ)[a]	$k_{C\text{-}M}$[b] $k_{C\text{-}m}$ (s^{-1})	$\Delta G^{\neq}_M$ $\Delta G^{\neq}_m$ (kJ mol^{-1})
2a	24	76	343	34.4 108.8	74.31 71.02
2b	26	74	343	36.3 103.3	74.15 71.17
	(SER-*s*-D-***a***) ⇆ (*s*-***s***) γ ε		T_C (K) ε + (β + γ)	$k_{C\text{-}M}$ $k_{C\text{-}m}$ (s^{-1})	$\Delta G^{\neq}_M$ $\Delta G^{\neq}_m$ (kJ mol^{-1})
3a	23.5	76.5	333	38.0 123.5	71.78 68.52
3b	21	79	333	38.6 145.1	71.74 68.07
3c	27	73	333	26.4 71.3	72.80 70.04

[a]*Signals providing coalescence (Table 1).* [b]*Kinetic data for the Major rotamer.* [c]*Kinetic data for the minor rotamer*

By replacement of the C-2-chlorine atom in *s*-triazines **2a-c** and **3a-c** with a bulky, basic and strong releasing piperazine unit, we expected that the resulting decreased π-deficiency of melamines **4a-c** and **5a-c** would diminish the partial double bond character of their C(*s*-triazine)-N(exocyclic) junctions to such an extent that the rotational phenomena would have been obscured. Nevertheless, at room temperature, essentially contrasting with other simpler melamines [20-26], rotamerism was detectable as classic "slow exchange status between unequally populated sites" [57] (Table 6, Fig. 2).

On ^{1}H timescale, the supporting number of broad N*H* singlets exhibited by the **D** and **SER** units (Supplementary Figs. 6a and 7a) did not correlate with the number of exchangeable sites because, as a typical example, the 2D-^{1}H,^{1}H-COSY chart of compound **4c** clearly disclosed four times an ax-N*H*-C*H*-5-e $^3J_{H,H}$

Table 6. Relevant (VT) ^{1}H NMR data and Temperature Gradients of melamines **4a-c** and **5a-c** (on 500 MHz timescale in [D_6]DMSO).

No.	Relevant δ_{NH} (ppm) values and multiplicity					TG[a]	TG
	T (K)	D-N*H*	SER-N*H*	Pip-N*H*	SER-O*H*	D-N*H*	SER-N*H*
4a	298	5.80, 5.70 (bs)	5.56 (bs)	4.77 (bs)		-4.8; -3.2	-2.0
	T_C = 313	5.59 (bs)	-	-			
	363	5.49 (d)[b]	5.43 (s)	4.54 (bs)			
4b	298	5.81, 5.68 (bs)	5.55, 5.44 (bs)	4.74 (bs)		-4.5, -2.5	-3.1, -1.4
	T_C = 313	5.65 (bs)	5.44 (bs)	-			
	363	5.52 (d)	5.35 (s)	4.54 (bs)			
4c	298	5.92, 5.81 (bs)	5.57, 5.49 (bs)	2.64 (s)	3.45 (s)	-5.6, -3.6	-2.5, -1.1
	T_C = 313	5.77 (bs)	5.48 (bs)	-	-		
	353	5.61 (d)	5.43 (s)	2.68 (s)	3.30 (bs)		
5a	298	6.77, 6.60 (bs)	5.71, 5.60 (bs)	4.84 (bs)		-9.1, -6.0	-2.9, -0.9
	T_C = 323	6.49 (bs)	5.62 (bs)	-			
	353	6.27 (bdd as bt)[c]	5.55 (s)	4.66 (bs)			
5b	298	6.82, 6.58 (bs)	5.59 (bs)	4.77 (bs)		-9.6, -5.3	-2.4
	T_C = 323	5.51 (bs)	-	-			
	353	6.29 (bdd as bt)	5.46 (s)	4.68 (bs)			
5c	303	6.93, 6.80, 6.69 (bs)	5.62 (bs)	3.65 (bs)	4.81 (bs)	-11.0, -8.4, -6.2	-1.8
	T_C = 323	6.60 (bs)	-	-	-		
	353	6.38 (bs)	5.53 (s)	3.00 (bs)	4.65 (bs)		

[a]As $(\Delta\delta_{NH} / \Delta T) \times 10^3$ (ppb K^{-1}). [b]Doublet with a typical $^3J_{H,H}$(ax-NH-CH-5-e) = 9.5 Hz in D (ax) N-ligand of series 4. [c]Broad doublet of doublets as broad triplet with a typical $^3J_{H,H}$(eq-CH_2-NH) = 5.5 – 6.0 Hz in D (eq) N-ligand of series 5.

coupling (Fig. 3; Supplementary Fig. 5). Hence, the two **D-N*H*** peaks of **4c** referred, in fact, to four environments, *i.e.,* a "hidden four terms rotational diastereomerism" about the same bonds C(-4, -6, *s*-triazine)-N(exocyclic). That is, although these junctions still remained two axes of diastereomerism as they were in chloro-precursors **2** and **3**, their discrete nature prevented us to establish unambiguously a topologic relationship between the rotameric species thus revealed.

As shown in Table 6, in melamines possessing two geminal hydroxymethyl groups, protons OH and Pip-N*H* exhibited a unique broad singlet, attributable to a mediated environment issued from a rapid intermolecular exchange, >C(CH_2OH)$_2$ ⇆ *H*N-Pip. It follows that, for compounds **4a**, **4b**, **5a** and **5b**, one can presume a polymeric acid-base self-assembly, still existent at 80-90°C. In contrast, in the case of melamines **4c** and **5c**, it was very likely that the internal association of their three geminal hydroxymethyl groups prevailed against any implication in a similar external affiliation. Accordingly, only in TRIS (**c**) based derivatives **4c** and **5c**, different δ_{NH} values, OH and Pip-N*H*, were located.

Not only that ^{13}C NMR data supported but also completed the ^{1}H assignments.

Thus, while on ^{13}C timescale at least two sets of peaks for almost all **SER** or **D** *C*-environments were detected, fewer rotameric sites we observed in series **5** with respect to **4**. In this context, the bond C(*s*-triazine)-N(piperazine) was partial double as well, an authentic axis of prodiastereomerism, since either piperazine positions C-α' *vs*. -α" or C-β' *vs*. -β", even both, were diastereotopic in the majority of compounds (Fig. 2; Supplementary Figs. 6b and 7b).

In piperazine *N*-ligand, the δ_C values decreasing order as $\delta_{C\text{-}\beta} > \delta_{C\text{-}\alpha}$ (Fig. 2) was, in its turn, consistent with the acid-base participation of the Pip-N*H* sequence (*vide supra*). Moreover, the same C-β > C-α deshielding in melamines **4c** and **5c** indicated their piperazine *N*-ligand being, in these cases, an acid-base partner with the traces of water in [D_6]DMSO. It is noteworthy that, in comparison with the present "monomeric" melamines **4** and **5**, previously reported by us C-4(') , -6(') identically substituted dimeric melamines with the same *N*-ligands, **SER**(**a**-**c**) [2], **D** (**ax**) or **D** (**eq**) [1], the piperazine linker had all *C*-positions isochronous and notably located upfield, 41.7 – 42.8 ppm.

3.2.2.2. Reaching the fast free rotational status

As expected, upon heating to 80-90°C, the final line-shapes of signals **D-N*H*** (unique sharp doublet or broad triplet) and **SER-N*H*** (unique sharp singlet) (Fig. 2) showed our melamines becoming a single mediated structure, in a fast freely rotating status about all connections C(*s*-triazine)-N(exocyclic).

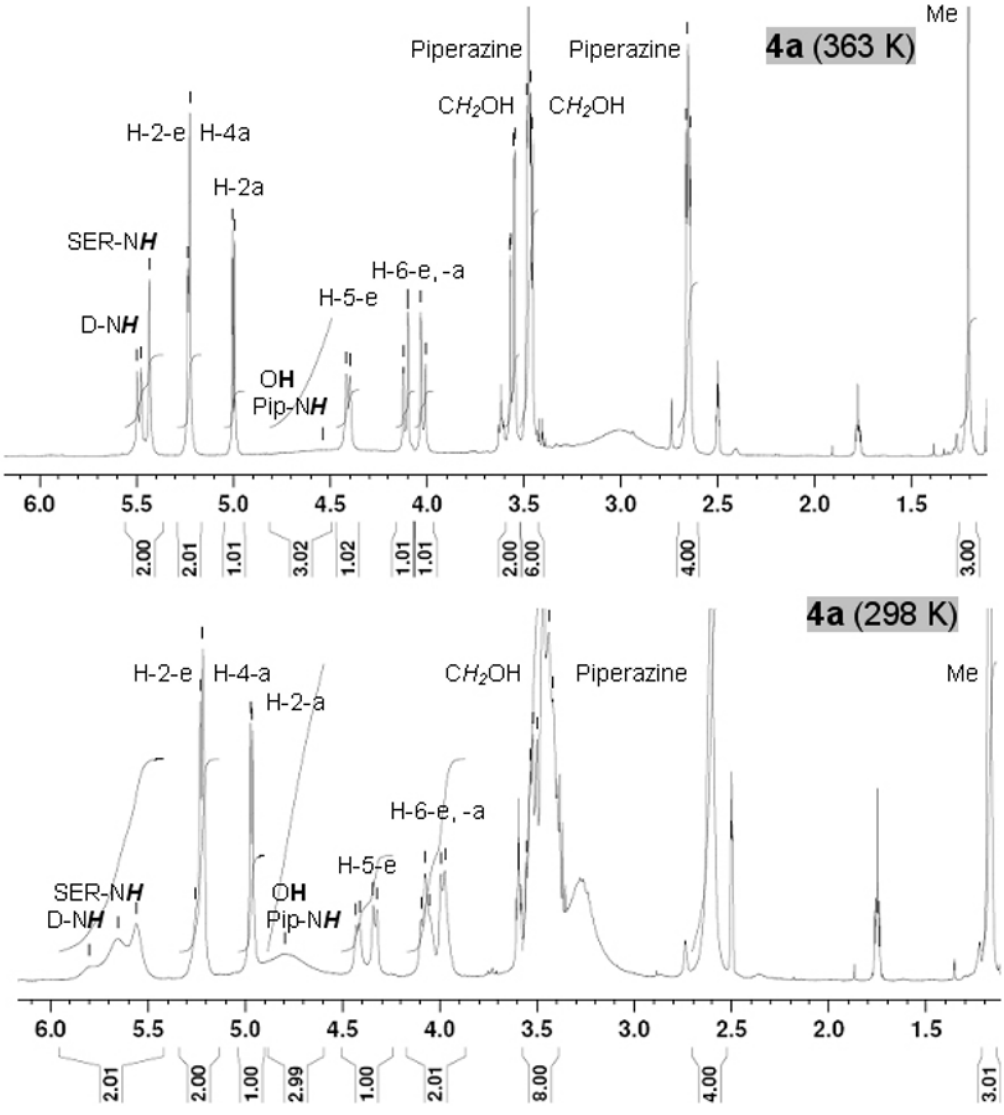


Figure 2. ^{1}H NMR temperature evolution of compound **4a** (on 500 MHz time scale in [D_6]DMSO); fast intermolecular acid-base exchanges in melamines **4a-c** and **5a-c** on ^{1}H, ^{13}C NMR timescales; (pro)diastereomerism about the bonds C(s-triazine)-N(exocyclic).

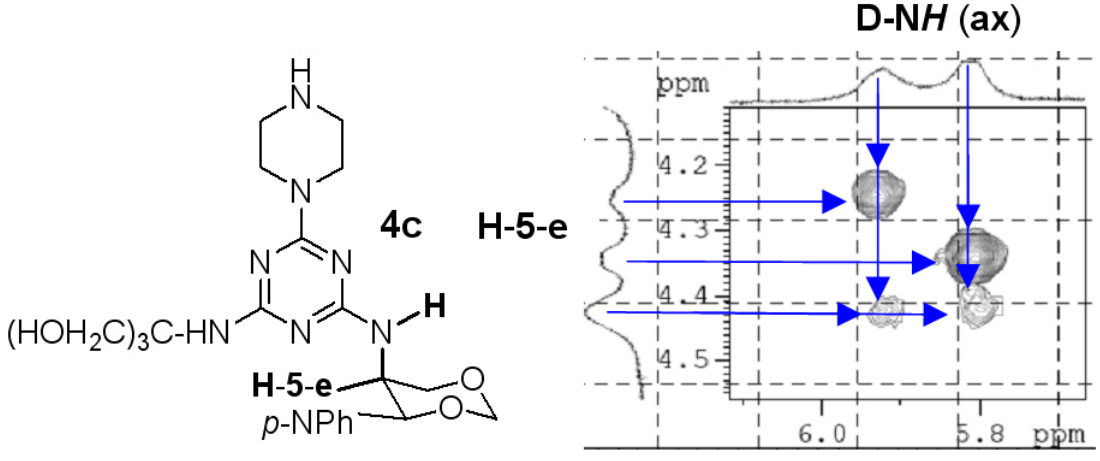


Figure 3. Detail from 2D-^{1}H,^{1}H-COSY Chart of compound **4c** (on 500 MHz time scale in [D_6]DMSO at 298 K).

The temperature dependent dynamic behaviour needs some comments:

i) The NH coalescences occurred almost simultaneously for **D** and **SER** *N*-ligands. Higher T_C values (+10 K) defined evolution of melamines **5a**-**c** against **4a**-**c** suggesting a more stable ground states of equatorially anchored derivatives (Table 6).

iii) Indeed, examination of TG values revealed the major contribution of the **D** *N*-ligands type of linkage to the above dissimilarity. Thus, as a consequence of the melamines' diminished π-deficiency, TGs of **SER-N*H*** (**a**-**c**) groups notably increased reaching very similar values (Tables 1, 2 and 6). They denoted a more important serinolic NH…OH internal hydrogen bonding than in the chloro-precursors. This fact was common, regardless series **4** or **5**. On the contrary, **D-N*H*** (**ax**) TGs in melamines **4a**-**c** were by far less negative than those of **D-N*H*** (**eq**) in **5a**-**c** (Table 6). The latter had about the same magnitude as in the corresponding most π-deficient precursors **3a**-**c** (Table 2). In addition, the noticeable downfield **D-N*H*** resonances in series **5** *vs.* **4** prompted us to conclude that this deshielding was due to a stronger chelation **D** (**eq**)**-N*H***…O=SMe_2 favoured by the sterically less crowded equatorial amino-anchorage. It was responsible for the higher stabilisation of the ground state of melamines **5a**-**c** with respect to axially built **4a**-**c**.

4. Conclusions

A clean and efficient access to highly elaborated enantiopure amino-*s*-triazines based on (phenyl)serinols was described. The final *N,N'N"*-unsymmetrically substituted melamines can be seen as valid building-blocks for iterative synthesis. At room temperature, regardless the π-deficiency extent of the *s*-triazine core, all compounds exhibited a four terms (pro) diastereomerism about the C(*s*-triazine)-N(exocyclic) partial double bonds. In chlorodiamino-*s*-triazines, both rotamerism incidence and its deblocking were dictated by i) the global molecular polarity and solvation of serinolic "*open-chain*" units then, ii) in a two step tandem, by the stereochemistry of the "*closed-chain*" units amino-anchorage, equatorial or axial, to the *s*-triazine core. As an overall result of these influences, chlorodiamino-*s*-triazines could completely activated about the bond C(*s*-triazine)-N("*closed-chain*" unit) only. In the melamines series, an intermolecular acid-base exchange self-assembled the terms possessing two geminal hydroxymethyl units at the periphery in partnership with the piperazine NH-*termini* group. Complete rotational deblocking of melaminic rotamers indicated the major influence of the solvent-"*closed-chain*" unit interactions in stabilizing the ground state of equatorially *vs.* axially connected derivatives.

Acknowledgements

The financial support from *Romanian National Council for Development and Innovation* Grant PN-II-ID-PCE-2011-3-0128 is gratefully acknowledged. OANA MOLDOVAN thanks for "***Investing in people!*** Ph.D. scholarship, Project co-financed by the SECTORAL OPERATIONAL PROGRAM FOR HUMAN RESOURCES DEVELOPMENT 2007 – 2013 **Priority Axis 1.** "Education and training in support for growth and development of a knowledge based society" **Key area of intervention 1.5**: Doctoral and post-doctoral programs in support of research. Contract no.: **POSDRU/88/1.5/S/60185** – "INNOVATIVE DOCTORAL STUDIES IN A KNOWLEDGE BASED SOCIETY" Babeş-Bolyai University, Cluj-Napoca, Romania". The computational centre of the University of Reims Champagne-Ardenne (ROMEO, http://www.romeo2.fr) is acknowledged for the CPU time donated.

References

[1] M. Fazekas, M. Pintea, P. Lameiras, A. Lesur, C. Berghian, I. Silaghi-Dumitrescu, N. Plé, M. Darabantu, Eur. J. Org. Chem. 14, 2473 (2008)
[2] M. Pintea, M. Fazekas, P. Lameiras, I. Cadis, C. Berghian, I. Silaghi-Dumitrescu, F. Popa, C. Bele, N. Plé, M. Darabantu, Tetrahedron 64, 8851 (2008)
[3] M. Darabantu, M. Pintea, M. Fazekas, P. Lameiras, C. Berghian, I. Delhom, I. Silaghi-Dumitrescu, N. Plé, A. Turck, Letters in Organic Chemistry 3, 905 (2006)
[4] M. Fazekas, M. Darabantu, M. Pintea, P. Lameiras, C. Bele, C. Berghian, N. Plé, Heterocyclic Commun. 12, 151 (2006)
[5] M. Pintea, M. Darabantu, M. Fazekas, P. Lameiras, C. Berghian, I. Delhom, C. Bele, N. Plé, Heterocyclic Commun. 12, 135 (2006)
[6] V. Lates, D. Gligor, M. Darabantu, L.M. Muresan, J. Appl. Electrochem. 37, 631 (2007)
[7] C. Bele, M. Darabantu, C.T. Matea, M. Pintea, M. Fazekas, C. Berghian, Buletin USAMV-CN 61, 194 (2005)
[8] C. Bele, M. Darabantu, M. Muntean, M. Pintea,

M. Fazekas, C. Berghian, D. Lazar, Buletin USAMV-CN 60, 1454 (2004)
[9] M. Darabantu, Curr. Org. Synth. 7, 120 (2010)
[10] M. Darabantu, Curr. Org. Synth. 7, 235 (2010)
[11] D.A. Tomalia, Aldrichimica Acta 37, 39 (2004)
[12] M.B. Steffensen, E.E. Simanek, Angew. Chem. Int. Ed. 43, 5178 (2004)
[13] M.B. Steffensen, E. Hollink, F. Kuschel, M. Bauer, E.E. Simanek, J. Polym. Sci. Part A: Polymer Chemistry 44, 3411 (2006)
[14] H.L. Crampton, E.E. Simanek, Polym. Int. 56, 489 (2007)
[15] E.E. Simanek, H. Abdou, S. Lalwani, J. Lim, M. Mintzer, V. J. Venditto, B. Vittur, Proc. R. Soc. A 466, 1445, (2010)
[16] X.C. Moreno, E.E. Simanek, Macromolecules 41, 4108 (2008)
[17] T. Drakenberg, S. Forsen, Chem. Commun. 21, 140 (1971)
[18] S.S. Mirvish, P. Gannett, D.M. Babcook, D. Williamson, S.C. Chen, D.D. Weisenburger, J. Agric. Food Chem. 39, 1205 (1991)
[19] I. Willner, J. Rosengaus, Y. Eichen, J. Phys. Org. Chem. 6, 29 (1993)
[20] A.R. Katritzky, I. Ghiviriga, D.C. Oniciu, A. Barkock, J. Chem. Soc. Perkin Trans. 2. 4, 785 (1995)
[21] A.R. Katritzky, I. Ghiviriga, P.G. Steel, D.C. Oniciu, J. Chem. Soc. Perkin Trans. 2. 3, 443 (1996)
[22] I. Ghiviriga, D.C. Oniciu, Chem. Commun. 22, 2718 (2002)
[23] M. Amm, N. Platzer, J. Guilhem, J.P. Bouchet, J.P. Volland, Magn. Reson. Chem. 36, 587 (1998)
[24] M. Amm, N. Platzer, J.P. Bouchet, J.P. Volland, Magn. Reson. Chem. 39, 77 (2001)
[25] H.E. Birkett, R.K. Harris, P. Hodgkinson, K. Carr, M.H. Charlton, J.C. Cherryman, A.M. Chippendale, R.P. Glover, Magn. Reson. Chem. 38, 504 (2000)
[26] H.E. Birkett, J.C. Cherryman, A.M. Chippendale, J.O.S. Evans, R.K. Harris, M. James, I.J. King, G.Mc. Pherson, Magn. Reson. Chem. 41, 324 (2003)
[27] M. Darabantu, C. Maiereanu, G. Plé, C. Berghian, C. Condamine, Y. Ramondenc, Heterocyclic Commun. 7, 593 (2001)
[28] M. Darabantu, G. Plé, S. Mager, C. Puscas, E. Cotora, Tetrahedron 53, 1909 (1997)
[29] M. Darabantu, S. Mager, G. Plé, C. Puscas, Heterocycles 41, 2327 (1995)
[30] M. Darabantu, S. Mager, C. Puscas, M. Bogdan, E. Cotora, G. Plé, I. Bratu, Revue Roumaine de Chimie 39, 955 (1994) (In French)
[31] R.C. Galesworthy, R.M. Show, B.C. Smith, J. Chem. Soc. 1507 (1962)
[32] R.M. Show, P.J. Ward, J. Chem. Soc. 5446 (1965)
[33] B.I. Stepanov, G.I. Migachev, E.F. Ilina, Zh. Obshch. Khim. 37, 2140 (1967) (In Russian)
[34] R.M. Show, P.J. Ward, J. Chem. Soc. 12, 1431 (1968)
[35] G.I. Migachev, E.F. Ilina, B.I. Stepanov, Zh. Obsch. Khim. 38, 1370 (1968) (In Russian)
[36] R.M. Show, P.J. Ward, J. Chem. Soc. 6, 596 (1969)
[37] G. Boncic-Caricic, Z.D. Tadic, M.D. Muskatirovic, J. Serb. Chem. Soc. 59, 929 (1994)
[38] (a) N.D. Reddy, A.J. Elias, N. Ashwani-Vij, J. Chem. Research (S) 9, 504 (1998); (b) J. Chem. Research (M) 2033 (1998)
[39] B. Kolesinska, Z.J. Kaminski, Tetrahedron 65, 3573 (2009)
[40] L.-L. Lai, L.-Y. Wang, C.-H. Lee, C.Y. Lin, K.-L. Cheng, Org. Lett. 8, 1541 (2006)
[41] L.-L. Lai, C.-H Lee, L.-Y Wang, K.L. Cheng, H.-F, J. Org. Chem. 73, 485 (2008)
[42] W. Zhang, E.E. Simanek, Org. Lett. 2, 843 (2000)
[43] W. Zhang, D.T. Nowlan, L.M. Thomson, M.W. Lackowski, E.E. Simanek, J. Am. Chem. Soc. 123, 8914, (2001)
[44] W. Zhang, E.E. Simanek, Tetrahedron Lett. 42, 5355, (2001)
[45] W. Zhang, S.O. Gonzalez, E.E. Simanek, Macromolecules 35, 9015 (2002)
[46] A.P. Umali, E.E. Simanek, Org. Lett. 5, 1245 (2003)
[47] W. Zhang, S.E. Tichy, L.M. Perez, C.G. Maria, P.A. Lindahl, E.E. Simanek, J. Am. Chem. Soc. 125, 5086 (2003)
[48] E.J. Acosta, Y. Deng, G.N. White, J.B. Dixon, K.J. Mc Innes, S.A. Senseman, A.S. Frantzen, E.E. Simanek, Chem. Mater. 15, 2903 (2003)
[49] A.P. Umali, L.H. Crampton, E.E. Simanek, J. Org. Chem. 72, 9866 (2007)
[50] S. Yooa, S. Yeua, R.L. Sherman, E.E. Simanek, D.F. Shantza, D.M.J. Ford, Membrane Sci. 334, 16 (2009)
[51] S. Lalwani, V.J. Venditto, A. Chouai, E.G. Rivera, S. Shaunak, E.E. Simanek, Macromolecules 42, 3152 (2009)
[52] F. Popa, P. Lameiras, E. Henon, O. Moldovan, A. Martinez, C. Batiu, Y. Ramondenc, M. Darabantu, Can. J. Chem. 89, 1207 (2011)
[53] E.L. Eliel, H.S. Wilen, Stereochemistry of the Organic Compounds (John Wiley & Sons, New York, Chichester, Brisbane, Toronto, Singapore, 1994) 221–239, 488–507, 678, 788, 1210
[54] M.J.O. Anteunis, D. Tavernier, F. Borremans, Heterocycles 4, 293 (1976)

[55] J. Lim, E.E. Simanek, Mol. Pharmaceutics 2, 273 (2005)
[56] H. Kessler, Angew. Chem. Int. Ed. Engl. 21, 512 (1982)
[57] H. Friebolin, Basic One- and Two Dimensional NMR Spectroscopy (VCH Verlagsgesellschaft, VCH: Weinheim, New York, 1991) 53, 93, 131, 132, 263–291
[58] R.M. Silverstein, F.X. Webster, D.J. Kiemle, Identification spectrométrique de composes organiques, 2nd edition (De Boeck & Larcier s.a., Bruxelles, 2007) 150-155 (In French)
[59] H. Shanan-Atidi, R.H. Bar Eli, J. Phys. Chem. 74, 961 (1970)
[60] H.S. Gutowski, C.H. Holm, J. Chem. Phys. 25, 1228 (1956)
[61] C. Berghian, P. Lameiras, L. Toupet, E. Condamine, N. Plé, A. Turck, C. Maiereanu, M. Darabantu, Tetrahedron, 62, 7319 (2006)
[62] M. Darabantu, C. Maiereanu, I. Silaghi-Dumitrescu, L. Toupet, E. Condamine, Y. Ramondenc, C. Berghian, G. Plé, N. Plé, Eur. J. Org. Chem. 12, 2644 (2004)